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☐ 1. Document ID: US 6051376 A

L1: Entry 1 of 3 File: USPT Apr 18, 2000

US-PAT-NO: 6051376
DOCUMENT-IDENTIFIER: US 6051376 A

TITLE: Uses of mda-6

DATE-ISSUED: April 18, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Fisher; Paul B.	Scarsdale	NY	N/A	N/A
Jiang; Hongping	New York	NY	N/A	N/A

US-CL-CURRENT: 435/6; 435/69.1, 436/501, 514/2, 514/44

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 5783182 A

L1: Entry 2 of 3 File: USPT Jul 21, 1998

US-PAT-NO: 5783182
DOCUMENT-IDENTIFIER: US 5783182 A

TITLE: Method for identifying metastatic sequences

DATE-ISSUED: July 21, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Thompson; Timothy C.	Houston	TX	N/A	N/A

US-CL-CURRENT: 424/93.21; 435/375, 435/467, 435/6, 435/69.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 3. Document ID: JP 2000513805 W, WO 9742222 A1, AU 9727077 A, EP 898580 A1

L1: Entry 3 of 3 File: DWPI Oct 17, 2000

DERWENT-ACC-NO: 1997-558909
DERWENT-WEEK: 200056

TITLE: Assays for modulators of cell growth - by screening for the ability of a compound to modulate interaction or binding between p21 and cyclin D1 and/or Cdk4

INVENTOR: BALL, K L; LANE, D P

PRIORITY-DATA: 1996GB-0021314 (October 9, 1996), 1996GB-0009521 (May 8, 1996)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
JP 2000513805 W	October 17, 2000	N/A	085	G01N033/15
WO 9742222 A1	November 13, 1997	E	105	C07K014/47
AU 9727077 A	November 26, 1997	N/A	000	C07K014/47
EP 898580 A1	March 3, 1999	E	000	C07K014/47

INT-CL (IPC): A61K 31/7088; A61K 38/00; A61K 38/17; A61K 45/00; A61K 48/00; A61P 35/00; A61P 43/00; C07K 7/08; C07K 14/47; G01N 33/15; G01N 33/50; G01N 33/566; G01N 33/68

Generate Collection

Terms	Documents
p21 same cyclin same compound	3

Display 10 Documents, starting with Document: 3

Display Format: CIT Change Format

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FILE 'HOME' ENTERED AT 10:12:57 ON 06 MAR 2001

=> file medline biosis embase caplus uspatfull

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                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

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=> s p21 (p) cyclin (p) cdk

L1         1894 P21 (P) CYCLIN (P) CDK

=> s p21 (p) cyclin (p) ientif?

L2            0 P21 (P) CYCLIN (P) IENTIF?

=> s p21 (p) cyclin (p) identif?\

L3          630 P21 (P) CYCLIN (P) IDENTIF?\

=> s p21 (p) cyclin (p) identif? (p) screen?

L4           43 P21 (P) CYCLIN (P) IDENTIF? (P) SCREEN?

=> dup rem l4

PROCESSING COMPLETED FOR L4
L5            18 DUP REM L4 (25 DUPLICATES REMOVED)

=> d l5 total ibib kwic


L5   ANSWER 1 OF 18  CAPLUS  COPYRIGHT 2001 ACS
ACCESSION NUMBER:         2000:742246  CAPLUS
DOCUMENT NUMBER:          133:291954
TITLE:                    An inducible expression vector for the p21
                          cyclin-dependent kinase inhibitor and its use in
                          identifying genes regulated by p21
INVENTOR(S):              Chang, Bey-Dih; Roninson, Igor B.
PATENT ASSIGNEE(S):       Board of Trustees of the University of Illinois, USA
SOURCE:                   PCT Int. Appl., 119 pp.
                          CODEN: PIXXD2
```

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000061751	A1	20001019	WO 2000-US9286	20000407

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-128676 19990409
US 1999-449589 19991129

REFERENCE COUNT: 12
REFERENCE(S):
(3) Chang, B; ONCOGENE 2000, V19(17), P2165 CAPLUS
(5) Chang, B; PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA 2000, V97(8), P4291 CAPLUS
(6) Hsiao, M; BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS 1997, V233, P329 CAPLUS
(7) Johnson, M; MOLECULAR CARCINOGENESIS 1994, V11(2), P59 CAPLUS
(8) Nakanishi, M; THE EMBO JOURNAL 1995, V14(3), P555 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT Drug **screening**
(for effectors of **p21**; inducible expression vector for **p21 cyclin**-dependent kinase inhibitor and its use in **identifying** genes regulated by **p21**)
IT Apoptosis
Cell proliferation
(**p21**-dependent, **screening** for effectors of for therapeutic use; inducible expression vector for **p21 cyclin**-dependent kinase inhibitor and its use in **identifying** genes regulated by **p21**)
IT Promoter (genetic element)
RL: BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**p21**-responsive, anal. of, **screening** for effectors of; inducible expression vector for **p21 cyclin**-dependent kinase inhibitor and its use in **identifying** genes regulated by **p21**)
IT Cell aging
(**screening** for inhibitors of; inducible expression vector for **p21 cyclin**-dependent kinase inhibitor and its use in **identifying** genes regulated by **p21**)

L5 ANSWER 2 OF 18 USPATFULL
ACCESSION NUMBER: 2000:47033 USPATFULL
TITLE: Uses of mda-6
INVENTOR(S): Fisher, Paul B., Scarsdale, NY, United States
Jiang, Hongping, New York, NY, United States
PATENT ASSIGNEE(S): The Trustees of Columbia University in the City of New York, New York, NY, United States (U.S. corporation)

	NUMBER	DATE	
PATENT INFORMATION:	US 6051376	20000418	
APPLICATION INFO.:	US 1994-316537	19940930	(8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1996-143576, filed on 27 Oct 1996, now patented, Pat. No. US 5643761
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Marschel, Ardin H.
LEGAL REPRESENTATIVE: White, John P.Cooper & Dunham LLP
NUMBER OF CLAIMS: 8
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 63 Drawing Figure(s); 45 Drawing Page(s)
LINE COUNT: 9039
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD Recent studies are providing new insights into the mode of action of **p21**. The **p21** protein was originally **identified** as part of quaternary **cyclin** D complexes in human diploid fibroblasts, that also possess **cyclin**-dependent kinases (CDK) and proliferating cell nuclear antigen (PCNA) (Xiong et al., 1992). Subsequent studies demonstrated that **p21** and PCNA can form multiple quaternary complexes with all **cyclins** and CDKs in normal human fibroblasts, but not in virally transformed cells (Xiong et al., 1993a). **p21** has also been shown to associate with and inhibit the activity of all **cyclin**-CDK enzymes (Xiong et al., 1993b; Harper et al., 1993; Gu et al., 1993). Recent experiments demonstrate that **p21** can directly complex with and inhibit PCNA suggesting that this protein may be a critical regulator of DNA replication, DNA repair and cell cycle machinery (Waga et al., 1994). The importance of **p21** in cell cycle and growth control has been reinforced by the independent isolation of this gene by virtue of its. . . induction by the tumor suppressor p53 [WAF1, (El-Deiry et al., 1993)], as a direct regulator of CDK2 using the two-hybrid **screening** technique [CIP1, Harper et al., 1993), as a cDNA from senescent cells with the ability to inhibit the ability of. . . a human melanoma cell library using subtraction hybridization (mda-6, Jiang & Fisher, 1993; Jiang et al., 1994). The level of **p21** has been shown to vary depending on the specific stage of the cell cycle (Li et al., 1994). In IMR90 normal diploid fibroblast cells released from serum starvation, the levels of **p21** are maximum immediately after serum stimulation, start to decrease as cells reach the G1/S boundary, display lowest levels during S. . . cells leave the S phase and enter the G2 and M phase (Li et al., 1994). These observations indicate that **p21** may contribute to both the G1/S and the G2/M checkpoint pathways. The interaction of **p21** with **cyclin** and CDK during the cell cycle is not random, but rather occurs when the specific **cyclin**-CDK enzyme is reputed to function (Li et al., 1994). Moreover, the increased level of **p21** in quiescent and terminally differentiated cells suggests that this protein may play a crucial role in preventing these cells from. . .

DETD . . . and differentiation inducer treated HO-1 human melanoma cDNA libraries (Jiang & Fisher, 1993). Using this strategy, an mda-6 cDNA was **identified** in a differentiation inducer (IFN-.beta.+MEZ) treated subtracted HO-1 human melanoma library that displays differential expression as a function of IFN-.beta.+MEZ induced growth arrest and terminal differentiation (Jiang & Fisher, 1993; Jiang et al., 1994a). By **screening** a differentiation inducer-treated HO-1 cDNA library (Jiang & Fisher, 1993) and using rapid amplification of cDNA ends (RACE) (Frohman et. . . CAP20 (Gu et al., 1993) and SDI1 (Noda et al., 1994) (FIG. 30). These genes encode the ubiquitous inhibitor of **cyclin** dependent kinases, **p21**.

L5 ANSWER 3 OF 18 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 1
ACCESSION NUMBER: 2000217019 EMBASE
TITLE: Association between polymorphism in p21(Waf1/Cip1)

cyclin-dependent kinase inhibitor gene and human oral cancer.

AUTHOR: Ralhan R.; Agarwal S.; Mathur M.; Wasylyk B.; Srivastava A.

CORPORATE SOURCE: R. Ralhan, Department of Biochemistry, All India Inst. of Medical Sciences, Ansari Nagar, New Delhi 110029, India. rralhan@medinst.ernet.in

SOURCE: Clinical Cancer Research, (2000) 6/6 (2440-2447).
Refs: 25
ISSN: 1078-0432 CODEN: CCREF4

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 016 Cancer

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The **cyclin**-dependent kinase inhibitor gene **p21** (Waf1/Cip1) plays a central role in inducing cellular growth arrest, terminal differentiation, and apoptosis. Alterations in this gene may adversely affect regulation of these processes and increase susceptibility for cancer. We have recently reported a novel polymorphism in the **p21**(Waf1/Cip1) gene in the Indian population and its association with esophageal cancer. An A.fwdarw.G transition at codon 149 resulted in amino acid substitution from aspartate to glycine in the proliferating cell nuclear antigen binding COOH-terminal domain of **p21** (Waf1/Cip1) that may affect PCNA-**p21**(Waf1/Cip1) interactions, thereby affecting regulation of cellular proliferation, and may increase susceptibility for development of cancer. In a parallel study in our laboratory, we searched for putative **p21**((Waf1/Cip1) mutations in oral premalignant and malignant lesions. No somatic mutation was detected in exon 2 of **p21**(Waf1/Cip1). Interestingly, a codon 149 polymorphism variant (A.fwdarw.G) was **identified** in 11 of 30 (37%) premalignant lesions (7 of 19 hyperplastic lesions and 4 of 11 dysplastic lesions) and 11 of 30 (37%) squamous cell carcinomas (SCCs). This codon 149 variant was also **identified** in paired lymphocytes of all of the patients with premalignant lesions and SCCs harboring the variant allele, suggesting the occurrence of a polymorphism. Lymphocyte DNA isolated from 50 unrelated age- and gender-matched healthy subjects was **screened** for this polymorphism. Seven of 50 (14%) normal controls harbored the A.fwdarw.G codon 149 variant allele. Immunohistochemical analysis of **p21**(Waf1/Cip1) protein expression showed immunoreactivity in 19 of these 30 (63%) oral premalignant lesions and 16 of 30 (53%) SCCs. The. . . also in patients with premalignant lesions (P = 0.038), compared with normal controls; and (b) the significantly higher frequency of **p21**(waf1/cip1) variants (codon 149) in oral premalignant lesions (10 of 11 cases) and SCCs (11 of 11 cases) with wild-type p53. . . suggesting that this polymorphism affects the p53 pathway and may play a vital role in oral tumorigenesis. Furthermore, overexpression of **p21** protein in oral lesions harboring missense mutations in the p53 gene suggest a p53-independent role for **p21** in the pathogenesis of oral cancer.

L5 ANSWER 4 OF 18 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2000394207 EMBASE

TITLE: Inhibitors of cyclin-dependent kinases as anti-cancer therapeutics.

AUTHOR: Fischer P.M.; Lane D.P.

CORPORATE SOURCE: P.M. Fischer, Cyclacel Limited, Dundee Technopole, James Lindsay Place, Dundee DD1 5JJ, United Kingdom. pfischer@cyclacel.com

SOURCE: Current Medicinal Chemistry, (2000) 7/12 (1213-1245).
Refs: 148
ISSN: 0929-8673 CODEN: CMCHE7

COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Initiation, progression, and completion of the cell cycle are regulated by
various **cyclin**-dependent kinases (CDKs), which are thus critical for cell growth. Tumour development is closely associated with genetic alteration and deregulation of. . . may be useful anti-cancer therapeutics. Indeed, early results suggest that transformed and normal cells differ in their requirement for e.g. **cyclin**/CDK2 and that it may be possible to develop novel antineoplastic agents devoid of the general host toxicity observed with conventional. . . active-site inhibitors of CDKs have been studied; the main limitation with these ATP antagonists is kinase specificity for CDKs. However, **screening** of compound collections, as well as rational design based on enzyme-ligand
complex crystal structures, are now yielding pre-clinical candidates, particularly. . . purine and flavonoid analogues, with impressive potency and selectivity. Natural CDK inhibitors (CKIs), e.g. the tumour suppressor gene products p16(INK4), **p21**(WAF1), and p27(KIP1), form the starting point for the design of mechanism-based CDK inhibitors. A number of these small proteins have been dissected and inhibitory lead peptides amenable to peptidomimetic development have been **identified**. Conversion of these peptides into pharmaceutically useful molecules is greatly aided by the recent elucidation of CKI/CDK crystal and solution. . . being exploited for the purposes of inhibitor
design include: phosphorylation/dephosphorylation sites, macromolecular substrate binding site, CKS regulatory subunit binding sites, **cyclin**-binding site, cellular localisation domain, and destruction box. Finally, progress has recently been made in the application of antisense technology in. . .

L5 ANSWER 5 OF 18 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 1999290651 MEDLINE
DOCUMENT NUMBER: 99290651
TITLE: Proteasome inhibitors: a novel class of potent and effective antitumor agents.
AUTHOR: Adams J; Palombella V J; Sausville E A; Johnson J; Destree A; Lazarus D D; Maas J; Pien C S; Prakash S; Elliott P J
CORPORATE SOURCE: ProScript, Inc., Cambridge, Massachusetts 02139, USA.. jadams@proscript.com
SOURCE: CANCER RESEARCH, (1999 Jun 1) 59 (11) 2615-22.
Journal code: CNF. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199909
ENTRY WEEK: 19990901
AB . . . series of proteasome inhibitors, exemplified by PS-341, which we describe here. As determined by the National Cancer Institute in vitro **screen**, PS-341 has substantial cytotoxicity against a broad range of human tumor cells, including prostate cancer cell lines. The PC-3 prostate. . . PS-341. In vitro, PS-341 elicits proteasome inhibition, leading to an increase in the intracellular levels of specific proteins, including the **cyclin**-dependent kinase inhibitor, **p21**. Moreover, exposure of such cells to PS-341 caused them to accumulate in the G2-M phase of the cell cycle and. . . Studies also revealed that i.v. administration of PS-341 resulted in a rapid and widespread distribution of PS-341, with highest levels **identified** in the liver and gastrointestinal tract and lowest levels in the skin and muscle.
Modest levels were found in the. . .

L5 ANSWER 6 OF 18 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 1999403006 MEDLINE
DOCUMENT NUMBER: 99403006
TITLE: A genetic screen for modifiers of E2F in Drosophila melanogaster.
AUTHOR: Staehling-Hampton K; Ciampa P J; Brook A; Dyson N
CORPORATE SOURCE: Massachusetts General Hospital Cancer Center, Charlestown, Massachusetts 02129, USA.
CONTRACT NUMBER: GM-53203 (NIGMS)
SOURCE: GENETICS, (1999 Sep) 153 (1) 275-87.
Journal code: FNH. ISSN: 0016-6731.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY WEEK: 20000104
AB . . . in part by pRB, the protein product of the retinoblastoma tumor suppressor gene. Studies of tumor cells show that the p16(ink4a)/cdk4/ **cyclin** D/pRB pathway is mutated in most forms of cancer, suggesting that the deregulation of E2F, and hence the cell cycle,. . . cell-cycle control and may play a role in tumorigenesis. We used an E2F overexpression phenotype in the Drosophila eye to **screen** for modifiers of E2F activity. Coexpression of dE2F and its heterodimeric partner dDP in the fly eye induces S phases and cell death. We isolated 33 enhancer mutations of this phenotype by EMS and X-ray mutagenesis and by **screening** a deficiency library collection. The majority of these mutations sorted into six complementation groups, five of which have been **identified** as alleles of brahma (brm), moira (mor) osa, pointed (pnt), and polycephalon (poc). osa, brm, and mor encode proteins with. . . of a SWI/SNF chromatin-remodeling complex has an important impact on E2F-dependent phenotypes. Mutations in poc also suppress phenotypes caused by **p21**(CIP1) expression, indicating an important role for polycephalon in cell-cycle control.

L5 ANSWER 7 OF 18 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 1999208479 MEDLINE
DOCUMENT NUMBER: 99208479
TITLE: The mechanisms of death of an erythroleukemic cell line by p53: involvement of the microtubule and mitochondria.
AUTHOR: Kato M V
CORPORATE SOURCE: Molecular Oncology Laboratory, Tsukuba Life Science Center, The Institute of Physical and Chemical Research (RIKEN), Ibaraki, Japan.. mkato@rtc.riken.go.jp
SOURCE: LEUKEMIA AND LYMPHOMA, (1999 Mar) 33 (1-2) 181-6.
Journal code: BNQ. ISSN: 1042-8194.
PUB. COUNTRY: Switzerland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
AB . . . were cultured at 32 degrees C. In this process, p53 recovered the wild-type p53 function and the expression of the **p21** (waf1/cip1/sdi1), **cyclin** G1 and gadd45 genes was increased. However, no significant changes were detected in the expression of the mdm2, bcl-2, bax, fas and fasl genes, suggesting the existence of other genes associated with apoptosis. Genes up-regulated by p53 were **screened** by the mRNA differential display method. One of the up-regulated genes was **identified** as the elongation factor 1 alpha (EF-1 alpha) gene. EF-1 alpha is also a microtubule-severing protein. Upon the temperature-shift, the. . . of EF-1 alpha by p53 may

be a cause of the cell death. On the other hand, the function of **cyclin** G1 is not so clear despite the fact that 1-2-3 cells showed a significant increase of the **cyclin** G1 gene during the early stage of apoptosis. The yeast two-hybrid system was used to **identify cyclin** G1-associated proteins. One is a cytochrome c (Cyt c) oxidase subunit II (COXII). **Cyclin** G1 and COXII were co-immunoprecipitated from an extract of human osteosarcoma cell line that expressed high levels of **cyclin** G1. COX activity was also increased by temperature-shift in this cell line. The pattern of changes in COX activity was closely reflected by the expression of the **cyclin** G1 gene. **Cyclin** G1 and COXII associate physically with each other in vivo and that activation of COXII by binding to **cyclin** G1 upregulated by p53 may be associated with apoptosis. These two new pathways, p53-EF-1 alpha-microtubule-severing (-distortion of cytoskeleton) and p53-**cyclin** G1-COXII (-CytC, ATP-caspase-3 activation), may cooperate to induce apoptosis in this cell line.

L5 ANSWER 8 OF 18 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:550494 CAPLUS
DOCUMENT NUMBER: 129:172777
TITLE: P21CIP1 or p27KIP1 effects on the regulation of differentiation of human mesenchymal stem cells
INVENTOR(S): Connolly, Timothy J.
PATENT ASSIGNEE(S): Osiris Therapeutics, Inc., USA
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9835022	A1	19980813	WO 1998-US2137	19980205
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9861444	A1	19980826	AU 1998-61444	19980205
PRIORITY APPLN. INFO.:			US 1997-36917	19970206
			WO 1998-US2137	19980205

AB Disclosed is a method for distinguishing undifferentiated human mesenchymal stem cells (hMSCs) from partially or completely differentiated human mesenchymal cells. In accordance with the invention it has been discovered that the expression of **p21 Cyclin** Inhibitor Protein (p21CIP1) is upregulated in partially or completely differentiated human mesenchymal cells as compared to undifferentiated hMSCs. Thus, this provides a quality control marker and test or assay to confirm that hMSCs are truly undifferentiated. That the p21CIP1 gene is either not expressed in clearly undifferentiated hMSCs or is significantly upregulated in partially or completely differentiated human mesenchymal cells by mesenchymal lineage inducers provides a **screening** method for **identifying** previously unknown mesenchymal lineage inducers. Also disclosed is an assay to det. the competence of mesenchymal progenitor cells to differentiate, particularly for in vivo tissue repair and particularly with respect to the osteogenic lineage. The inventors have made this possible by their observation that, in cells at approx. 80% confluence in in vitro culture, p27 Kinase Inhibitor Protein (p27KIP1) expression levels are upregulated in differentiation competent mesenchymal stem cell as compared to differentiation incompetent mesenchymal stem cells.

L5 ANSWER 9 OF 18 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 1999003537 MEDLINE
DOCUMENT NUMBER: 99003537
TITLE: The p16(INK4A) protein and flavopiridol restore yeast cell growth inhibited by Cdk4.
AUTHOR: Moorthamer M; Panchal M; Greenhalf W; Chaudhuri B
CORPORATE SOURCE: Oncology Research, Novartis Pharma AG, Basel, Switzerland.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1998 Sep 29) 250 (3) 791-7.
Journal code: 9Y8. ISSN: 0006-291X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199901
ENTRY WEEK: 19990104
AB **Cyclin**-dependent kinase 4 (Cdk4) activity is misregulated in most cancers. Loss of Cdk4 regulation can occur through overexpression of Cdk4 catalytic subunit or its regulatory partner **cyclin** D1, or if the Cdk4-specific inhibitory protein p16(INK4A) is inactive. We have attempted to express the two human subunits, Cdk4 and **cyclin** D1, in the yeast Saccharomyces cerevisiae. Surprisingly, expression of Cdk4 alone, under control of the strong GAL promoter, inhibits cell growth. Coexpression of both subunits allows formation of an active Cdk4-**cyclin** D1 complex which accentuates growth arrest. In cells expressing Cdk4 only, growth is restored by overexpressing human Cdc37, a Cdk4-binding molecular chaperone. Interestingly, the effect of Cdk4 on yeast is also overcome by both p16- and **p21**-families of Cdk-inhibitory proteins. Moreover, flavopiridol, a compound which inhibits Cdk4 enzyme activity, restores cell division. The fact that p16(INK4A) and flavopiridol negate Cdk4-mediated suppression of yeast cell growth implies that this simple system can be used as a **screen** for **identifying** Cdk4-specific antagonists which may mimic p16(INK4A) in the cancer cell cycle. Copyright 1998 Academic Press.

L5 ANSWER 10 OF 18 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 1999107110 MEDLINE
DOCUMENT NUMBER: 99107110
TITLE: Analysis of the p21 gene in gliomas.
AUTHOR: Li Y J; Hoang-Xuan K; Zhou X P; Sanson M; Mokhtari K; Faillot T; Cornu P; Poisson M; Thomas G; Hamelin R
CORPORATE SOURCE: INSERM U434, Genetique des Tumeurs, CEPH, Paris, France.
SOURCE: JOURNAL OF NEURO-ONCOLOGY, (1998 Nov) 40 (2) 107-11.
Journal code: JCP. ISSN: 0167-594X.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
AB The **p21** gene encodes a **cyclin** dependent kinase inhibitor protein (**p21**) which has a tumor suppressive activity in a variety of tumor cell lines. Since, the **p21** gene is up-regulated by the p53 tumor suppressor gene, which is frequently mutated in gliomas, acting therefore in the same. . . gliomas (48 glioblastomas, 11 anaplastic astrocytomas, 10 low-grade astrocytomas, 12 oligodendrogliomas and mixed gliomas), were investigated for mutations in the **p21** coding sequence by denaturant gradient gel electrophoresis followed by sequencing. All these tumors have been previously **screened** for p53 mutations. Three different DNA variants were **identified** on codon 31 (17 cases), 27 (1 case) and 117 (1 case) and shown to be also present in matching. . . suggesting

they were polymorphisms. None of the tumors demonstrated a somatic mutation. No significant correlation between the presence of a **p21** variant and the p53 mutation tumor status was observed. In conclusion, mutation in the **p21** gene unlikely contributes to the development of gliomas.

L5 ANSWER 11 OF 18 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:746076 CAPLUS
DOCUMENT NUMBER: 128:18686
TITLE: Methods and means using p21WAF1 peptide fragments for inhibition of cdk4 activity
INVENTOR(S): Ball, Kathryn Lindsay; Lane, David Philip
PATENT ASSIGNEE(S): Cyclacel Limited, UK; Ball, Kathryn Lindsay; Lane, David Philip
SOURCE: PCT Int. Appl., 105 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9742222	A1	19971113	WO 1997-GB1250	19970508
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9727077	A1	19971126	AU 1997-27077	19970508
EP 898580	A1	19990303	EP 1997-920857	19970508
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2000513805	T2	20001017	JP 1997-529635	19970508
PRIORITY APPLN. INFO.:			GB 1996-9521	19960508
			GB 1996-21314	19961009
			WO 1997-GB1250	19970508

OTHER SOURCE(S): MARPAT 128:18686
AB P21WAF1 interacts with **cyclin** D1 and Cdk4. Peptide fragments of **p21** inhibit the interaction and/or affect Cdk4 activity. The peptides, deriv. peptides, and nonpeptidyl mimetics thereof are useful in affecting activity of Cdk4, such as RB phosphorylation, and cellular proliferation, indicative of therapeutic usefulness in treatment of tumors and other hyperproliferative disorders. Assay and **screening** methods allow **identification** of such modulators, esp. inhibitors, of Cdk4 activity.

L5 ANSWER 12 OF 18 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 97334867 MEDLINE
DOCUMENT NUMBER: 97334867
TITLE: Association between human cancer and two polymorphisms occurring together in the p21Waf1/Cip1 cyclin-dependent kinase inhibitor gene.
AUTHOR: Facher E A; Becich M J; Deka A; Law J C
CORPORATE SOURCE: Department of Human Genetics, University of Pittsburgh, PA 15261, USA.
SOURCE: CANCER, (1997 Jun 15) 79 (12) 2424-9.
Journal code: CLZ. ISSN: 0008-543X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer

Journals
ENTRY MONTH: 199708
ENTRY WEEK: 19970804
AB BACKGROUND: The **cyclin**-dependent kinase inhibitor gene p21Waf1/Cip1 plays a role in signaling cellular growth arrest. In response to DNA damage, **p21** is induced by the p53 gene, thereby playing a direct role in mediating p53-induced G1 arrest. Alterations in this gene. . . may adversely affect regulation of cellular proliferation and increase susceptibility for cancer. Two polymorphisms have previously been characterized in the **p21** gene: a C-->A transversion at codon 31 (ser-->arg) and a C-->T transition 20 nucleotides downstream from the 3' end of exon 3. METHODS: The codon 31 polymorphism in exon 2 of the **p21** gene was **identified** by restriction digestion (Alw26I) of products amplified by polymerase chain reaction (PCR). The polymorphism downstream from exon 3 of the **p21** gene was **identified** by single strand conformation polymorphism (SSCP) analysis of PCR amplified products and was confirmed by PstI enzyme restriction digestion. DNA. . . alleles were confirmed by direct DNA sequencing. The entire coding region and the promoter region (p53 binding domain) of the **p21** gene were **screened** for mutations by SSCP analysis or DNA sequencing. RESULTS: The two polymorphisms were found in 18 of 96 tumor samples lacking p53 alterations (18.8%). Nine of 54 prostate adenocarcinoma samples (16.7%) contained both **p21** variants, whereas 9 of 42 squamous cell carcinomas of the head and neck (21.4%) displayed both polymorphisms. Of the 110 controls examined, 10 (9.1%) had both alterations. Both **p21** polymorphisms occurred together in all samples examined and there was no indication of mutation in the coding region of the **p21** gene or in the p53 binding domain of the promoter region. CONCLUSIONS: These data suggest that **p21** gene variants may play a role in increased susceptibility for the development of some types of cancer. In the current. . .

L5 ANSWER 13 OF 18 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:261680 CAPLUS
DOCUMENT NUMBER: 129:77934
TITLE: Two-hybrid screening and the cell cycle
AUTHOR(S): Hannon, Gregory J.
CORPORATE SOURCE: Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 11724, USA
SOURCE: Yeast Two-Hybrid Syst. (1997), 183-196. Editor(s): Bartel, Paul L.; Fields, Stanley. Oxford University Press: New York, N. Y.
CODEN: 65YDA2
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review with 61 refs. The two-hybrid **screen** has been most often successful in the **identification** of stable, protein-protein interactions. Perhaps, because such interactions are prevalent among components of cell cycle control, cell cycle regulatory proteins have proven amenable to the two-hybrid approach. Here, the authors discusses three aspects of cell cycle control in which the two-hybrid technique has been of particular importance. These are the regulation of the G1/S transition by phosphorylation of pRb, global control of cell cycle progression by the **p21**/p27 family of **cyclin**-dependent kinase (CDK) inhibitors and the role of CDK-activating kinase (CAK) and KAP in the metab. of threonine ~160 phosphorylation.

L5 ANSWER 14 OF 18 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 8
ACCESSION NUMBER: 1997:75244 BIOSIS
DOCUMENT NUMBER: PREV199799381947
TITLE: WAF1/Cip1 gene polymorphism and expression in carcinomas of

the breast, ovary, and endometrium.
AUTHOR(S): Lukas, Jason; Groshen, Susan; Saffari, Bahman; Niu, Ning; Reles, Angela; Wen, Wen-Hsiang; Felix, Juan; Jones, Lovell A.; Hall, Frederick L.; Press, Michael F. (1)
CORPORATE SOURCE: (1) Dep. Pathol. Norris Cancer Cent., Mailslot 73, U.S.C. Sch. Med., 1441 Eastlake Ave., Los Angeles, CA 90033 USA
SOURCE: American Journal of Pathology, (1997) Vol. 150, No. 1, pp. 167-175.
ISSN: 0002-9440.
DOCUMENT TYPE: Article
LANGUAGE: English
AB. . . are potential sites for somatic alterations. WAF1/Cip1, also known as WAF1, Cip1, sdi1, or CAP20, codes for a 21-kd protein (**p21**-WAF1/Cip1), which was recently described as a universal inhibitor of **cyclins** and is thus critical in cell cycle control. Mutations in WAF1/Cip1 are potentially important in human malignancies because they could affect the control of the cell cycle. To understand whether mutations of WAF1/Cip1 occur in cancer, we **screened** 53 cases of invasive breast carcinoma, 35 cases of ductal carcinoma in situ (DCIS), 53 ovarian carcinomas-. and 47 endometrial carcinomas in the second exon of WAF1/Cip1 (90% of the open reading frame). **p21**-WAF1/Cip1 expression was characterized with immunohistochemistry. Cells from the blood of 21 normal individuals were also characterized using single-strand conformational polymorphism. . . DCIS of the breast (14%), 8 invasive ovarian carcinomas (15%), and 9 endometrial carcinomas (19%). In total, 209 samples were **screened**, and 38 cases (18.2%) had an altered codon 31. Each case with altered single-strand conformational polymorphism, analyzed by DNA sequencing. . . These results indicate that codon 31 is a polymorphic site and that the serine to arginine shift is a polymorphism. **p21**-WAF1/Cip1 expression, **identified** by immunohistochemistry, was found to vary in a pattern that depended both on the tissue type and on the presence. . .

L5 ANSWER 15 OF 18 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 97134670 MEDLINE
DOCUMENT NUMBER: 97134670
TITLE: A cyclin-dependent kinase inhibitor, Dacapo, is necessary for timely exit from the cell cycle during Drosophila embryogenesis.
AUTHOR: de Nooij J C; Letendre M A; Hariharan I K
CORPORATE SOURCE: Massachusetts General Hospital Cancer Center, Charlestown 02129, USA.
SOURCE: CELL, (1996 Dec 27) 87 (7) 1237-47.
Journal code: CQ4. ISSN: 0092-8674.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
OTHER SOURCE: GENBANK-U77937
ENTRY MONTH: 199704
ENTRY WEEK: 19970402
AB In a **screen** for genes that interact with the Rap1 GTPase, we have **identified** a Drosophila gene, dacapo (dap), which is a member of the **p21**/p27 family of cdk inhibitors. Unlike mammalian cdk inhibitors studied to date, dap is essential for normal embryonic development. Dacapo inhibits **cyclin**-cdk activity in vitro. Overexpressing dap during eye development interferes with cell cycle progression and interacts genetically with the retinoblastoma homolog (Rbf) and **cyclin** E. dap expression in embryos parallels the exit of cells from the cell cycle. dap mutant embryos delay the normal. . .

L5 ANSWER 16 OF 18 MEDLINE DUPLICATE 10

ACCESSION NUMBER: 95095079 MEDLINE
DOCUMENT NUMBER: 95095079
TITLE: Growth suppression by p18, a p16INK4/MTS1- and p14INK4B/MTS2-related CDK6 inhibitor, correlates with wild-type pRb function.
AUTHOR: Guan K L; Jenkins C W; Li Y; Nichols M A; Wu X; O'Keefe C L; Matera A G; Xiong Y
CORPORATE SOURCE: Department of Biological Chemistry, University of Michigan, Ann Arbor 48109-0606..
CONTRACT NUMBER: GM 51586 (NIGMS)
SOURCE: GENES AND DEVELOPMENT, (1994 Dec 15) 8 (24) 2939-52. Journal code: FN3. ISSN: 0890-9369.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U17074; GENBANK-U17075
ENTRY MONTH: 199503

AB The D-type **cyclin**-dependent kinases CDK4 and CDK6 are complexed with many small cellular proteins (p14, p15, p16, p18, and p20). We have isolated. . . corresponding to the MTS2 genomic fragment that encodes the CDK4- and CDK6-associated p14 protein. By use of a yeast interaction **screen** to search for CDK6-interacting proteins, we have also **identified** an 18-kD human protein, p18, that is a homolog of the **cyclin** D-CDK4 inhibitors p16 (INK4A/MTS1) and p14 (MTS2/INK4B). Both in vivo and in vitro, p18 interacts strongly with CDK6, weakly with CDK4, and exhibits no detectable interaction with the other known CDKs. Recombinant p18 inhibits the kinase activity of **cyclin** D-CDK6. Distinct from the **p21**/p27 family of CDK inhibitors that form ternary complexes with **cyclin**-CDKs, only binary complexes of p14, p16, and p18 were found in association with CDK4 and/or CDK6. Ectopic expression of p18. . .

L5 ANSWER 17 OF 18 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 11
ACCESSION NUMBER: 1994:534474 BIOSIS
DOCUMENT NUMBER: PREV199497547474
TITLE: A molecular definition of terminal cell differentiation in human melanoma cells.
AUTHOR(S): Jiang, Hongping; Lin, Jian; Fisher, Paul B. (1)
CORPORATE SOURCE: (1) Dep. Pathol. Urol., Comprehensive Cancer Cent./Inst. Cancer Res., Columbia Univ., Coll. Phys. Surg., PH STEM-10, 630 W. 168th St., New York, NY 10032 USA
SOURCE: Molecular and Cellular Differentiation, (1994) Vol. 2, No. 3, pp. 221-239. ISSN: 1065-3074.
DOCUMENT TYPE: General Review
LANGUAGE: English

AB. . . and express differentiation-related functions or irreversibly terminally differentiate by treatment with appropriate agents. This system represents a useful model for **identifying** and defining the roles of cellular genes in regulating growth, mediating specific biochemical pathways in differentiation, and inducing the irreversible loss of proliferative capacity associated with terminal cell differentiation. Using subtraction hybridization, cDNA clones have been **identified** that display differential expression as a function of growth arrest, treatment with chemotherapeutic and DNA-damaging agents, and terminal cell differentiation.. . . differentially expressed cDNAs have been termed melanoma differentiation-associated (mda) genes (41). Six cDNAs have been cloned during the initial library **screening** that represent differentially expressed genes not previously reported or ascribed specific functions and may therefore represent novel genes involved in.

. differentiation (41). One initially novel cDNA, mda-6, that displays increased expression in terminally differentiated human melanoma cells is identical to **p21**, a **cyclin**-dependent kinase inhibitor (47). **p21** is a critical cell cycle-regulating gene that has been cloned by a number of laboratories using different approaches and referred. . . WAF1 (49), and sdi1 (51). Our current approach, induction of terminal differentiation combined with subtraction hybridization, has proven useful for **identifying** genes critical to the maintenance of normal cellular physiology (growth, differentiation, and response to DNA damage) and genes relevant to. . .

L5 ANSWER 18 OF 18 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 94306519 MEDLINE
DOCUMENT NUMBER: 94306519
TITLE: p27, a novel inhibitor of G1 cyclin-Cdk protein kinase activity, is related to p21.
AUTHOR: Toyoshima H; Hunter T
CORPORATE SOURCE: Molecular Biology and Virology Laboratory, Salk Institute, La Jolla, California 92037.
CONTRACT NUMBER: CA14195 (NCI)
CA39780 (NCI)
SOURCE: CELL, (1994 Jul 15) 78 (1) 67-74.
Journal code: CQ4. ISSN: 0092-8674.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
OTHER SOURCE: GENBANK-U10440
ENTRY MONTH: 199410
AB Using a yeast interaction **screen** to search for proteins that interact with **cyclin** D1-Cdk4, we **identified** a 27 kDa mouse protein related to the **p21 cyclin**-Cdk inhibitor. p27 interacts strongly with D-type **cyclins** and Cdk4 in vitro and more weakly with **cyclin** E and Cdk2. In mouse fibroblasts, p27 is associated predominantly with **cyclin** D1-Cdk4. Recombinant p27 is a potent inhibitor of **cyclin** D1-Cdk4 and **cyclin** A-Cdk2 protein kinase activity and a weaker inhibitor of **cyclin** B1-Cdc2. Overexpression of p27 in Saos-2 cells causes G1 arrest. p27 protein levels do not change as serum-stimulated quiescent mouse fibroblasts progress through the cell cycle. p27 is identical to p27Kip1, a **cyclin**-Cdk inhibitor present in TGF beta-treated cells. p27 has the hallmarks of a negative regulator of G1 progression and may mediate. . .

=> d his

(FILE 'HOME' ENTERED AT 10:12:57 ON 06 MAR 2001)

FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS, USPATFULL' ENTERED AT 10:13:17 ON 06 MAR 2001
L1 1894 S P21 (P) CYCLIN (P) CDK
L2 0 S P21 (P) CYCLIN (P) IENTIF?
L3 630 S P21 (P) CYCLIN (P) IDENTIF?\
L4 43 S P21 (P) CYCLIN (P) IDENTIF? (P) SCREEN?
L5 18 DUP REM L4 (25 DUPLICATES REMOVED)

=> s p21 (p) cyclin (p) identif? (p) modula?

L6 41 P21 (P) CYCLIN (P) IDENTIF? (P) MODULA?

=> dup rem 16

PROCESSING COMPLETED FOR L6

L7 20 DUP REM L6 (21 DUPLICATES REMOVED)

=> s l5 or l7

L8 37 L5 OR L7

=> dup rem l8

PROCESSING COMPLETED FOR L8
L9 37 DUP REM L8 (0 DUPLICATES REMOVED)

=> d l9 total ibib kwic

L9 ANSWER 1 OF 37 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:742246 CAPLUS
DOCUMENT NUMBER: 133:291954
TITLE: An inducible expression vector for the p21 cyclin-dependent kinase inhibitor and its use in identifying genes regulated by p21
INVENTOR(S): Chang, Bey-Dih; Roninson, Igor B.
PATENT ASSIGNEE(S): Board of Trustees of the University of Illinois, USA
SOURCE: PCT Int. Appl., 119 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000061751	A1	20001019	WO 2000-US9286	20000407

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-128676 19990409
US 1999-449589 19991129

REFERENCE COUNT: 12
REFERENCE(S):
(3) Chang, B; ONCOGENE 2000, V19(17), P2165 CAPLUS
(5) Chang, B; PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA 2000, V97(8), P4291 CAPLUS
(6) Hsiao, M; BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS 1997, V233, P329 CAPLUS
(7) Johnson, M; MOLECULAR CARCINOGENESIS 1994, V11(2), P59 CAPLUS
(8) Nakanishi, M; THE EMBO JOURNAL 1995, V14(3), P555 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT Drug **screening**
(for effectors of **p21**; inducible expression vector for **p21** **cyclin**-dependent kinase inhibitor and its use in **identifying** genes regulated by **p21**)
IT Apoptosis
Cell proliferation
(**p21**-dependent, **screening** for effectors of for therapeutic use; inducible expression vector for **p21** **cyclin**-dependent kinase inhibitor and its use in **identifying** genes regulated by **p21**)

IT Promoter (genetic element)
RL: BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**p21**-responsive, anal. of, **screening** for effectors of; inducible expression vector for **p21 cyclin**-dependent kinase inhibitor and its use in **identifying** genes regulated by **p21**)
IT Cell aging
(**screening** for inhibitors of; inducible expression vector for **p21 cyclin**-dependent kinase inhibitor and its use in **identifying** genes regulated by **p21**)

L9 ANSWER 2 OF 37 USPATFULL
ACCESSION NUMBER: 2000:47033 USPATFULL
TITLE: Uses of mda-6
INVENTOR(S): Fisher, Paul B., Scarsdale, NY, United States
Jiang, Hongping, New York, NY, United States
PATENT ASSIGNEE(S): The Trustees of Columbia University in the City of New York, New York, NY, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 6051376	20000418
APPLICATION INFO.:	US 1994-316537	19940930 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1996-143576, filed on 27 Oct 1996, now patented, Pat. No. US 5643761
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Marschel, Ardin H.
LEGAL REPRESENTATIVE: White, John P.Cooper & Dunham LLP
NUMBER OF CLAIMS: 8
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 63 Drawing Figure(s); 45 Drawing Page(s)
LINE COUNT: 9039
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD Recent studies are providing new insights into the mode of action of **p21**. The **p21** protein was originally **identified** as part of quaternary **cyclin** D complexes in human diploid fibroblasts, that also possess **cyclin**-dependent kinases (CDK) and proliferating cell nuclear antigen (PCNA) (Xiong et al., 1992). Subsequent studies demonstrated that **p21** and PCNA can form multiple quaternary complexes with all **cyclins** and CDKs in normal human fibroblasts, but not in virally transformed cells (Xiong et al., 1993a). **p21** has also been shown to associate with and inhibit the activity of all **cyclin**-CDK enzymes (Xiong et al., 1993b; Harper et al., 1993; Gu et al., 1993). Recent experiments demonstrate that **p21** can directly complex with and inhibit PCNA suggesting that this protein may be a critical regulator of DNA replication, DNA repair and cell cycle machinery (Waga et al., 1994). The importance of **p21** in cell cycle and growth control has been reinforced by the independent isolation of this gene by virtue of its. . . induction by the tumor suppressor p53 [WAF1, (El-Deiry et al., 1993)], as a direct regulator of CDK2 using the two-hybrid **screening** technique [CIP1, Harper et al., 1993), as a cDNA from senescent cells with the ability to inhibit the ability of. . . a human melanoma cell library using subtraction hybridization (mda-6, Jiang & Fisher, 1993; Jiang et al., 1994). The level of **p21** has been shown to vary depending on the specific stage of the cell cycle (Li et al., 1994). In IMR90 normal diploid fibroblast cells released from serum starvation, the levels of **p21** are maximum immediately after serum stimulation, start to decrease as cells reach the G1/S boundary, display lowest levels during S. . . cells leave the S phase and enter the G2 and M phase (Li et al., 1994). These observations indicate that **p21** may contribute to both the G1/S and the G2/M checkpoint pathways. The interaction of **p21** with

cyclin and CDK during the cell cycle is not random, but rather occurs when the specific **cyclin**-CDK enzyme is reputed to function (Li et al., 1994). Moreover, the increased level of **p21** in quiescent and terminally differentiated cells suggests that this protein may play a crucial role in preventing these cells from. . .

DETD . . . and differentiation inducer treated HO-1 human melanoma cDNA libraries (Jiang & Fisher, 1993). Using this strategy, an mda-6 cDNA was

identified in a differentiation inducer (IFN-.beta.+MEZ) treated subtracted HO-1 human melanoma library that displays differential expression as a function of IFN-.beta.+MEZ induced growth arrest and terminal differentiation (Jiang & Fisher, 1993; Jiang et al., 1994a). By

screening a differentiation inducer-treated HO-1 cDNA library (Jiang & Fisher, 1993) and using rapid amplification of cDNA ends (RACE)

(Frohman et. . . CAP20 (Gu et al., 1993) and SDI1 (Noda et al., 1994)

(FIG. 30). These genes encode the ubiquitous inhibitor of **cyclin** dependent kinases, **p21**.

L9 ANSWER 3 OF 37 USPATFULL

ACCESSION NUMBER:	2000:7193 USPATFULL
TITLE:	CDC37 cell-cycle regulatory protein and uses related thereto
INVENTOR(S):	Gyuris, Jeno, Winchester, MA, United States Lamphere, Lou, Boston, MA, United States Draetta, Giulio, Milan, Italy
PATENT ASSIGNEE(S):	Mitotix, Inc., Cambridge, MA, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 6015692	20000118
APPLICATION INFO.:	US 1997-853733	19970509 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1996-625209, filed on 1 Apr 1996, now patented, Pat. No. US 5756671 which is a continuation-in-part of Ser. No. US 1995-466679, filed on 6 Jun 1995, now abandoned which is a continuation-in-part of Ser. No. US 1994-253155, filed on 2 Jun 1994, now patented, Pat. No. US 5691147

DOCUMENT TYPE:	Utility
PRIMARY EXAMINER:	Carlson, Karen Cochrane
LEGAL REPRESENTATIVE:	Vincent, Esq., Matthew P.; Halstead, David P.
NUMBER OF CLAIMS:	26
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	1 Drawing Figure(s); 1 Drawing Page(s)
LINE COUNT:	2905

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . the appended examples and in parent application U.S. Ser. No. 08/253,155, a CDK4-dependent interaction trap assay (ITS) was used to **identify** proteins that can associate with human CDK4. The present invention, as set out below, derives from the discovery that, in addition to **cyclins**, **p21**, p16, and PCNA, CDK4 is also associated with several other cellular proteins (hereinafter termed "CDK4-binding proteins" or "CDK4-BPs"), which associations. . . control various aspects of the kinases's activity, including both catalytic activity and substrate specificity. Thus, because each of the proteins **identified** by the subject ITS act close to the point of CDK4 process control, such as by channeling converging upstream signals. . . activity by directing divergent downstream signal propagation from CDK4, each protein is a potential therapeutic target for agents capable of **modulating** cell proliferation and/or

differentiation.

L9 ANSWER 4 OF 37 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000385928 EMBASE
TITLE: Inhibition of mitogenesis in Balb/c-3T3 cells by trichostatin A. Multiple alterations in the induction and activation of cyclin-cyclin-dependent kinase complexes.
AUTHOR: Wharton W.; Savell J.; Cress W.D.; Seto E.; Pledger W.J.
CORPORATE SOURCE: W. Wharton, Molecular Oncology Program, H. L. Moffitt Cancer Center, 12902 Magnolia Dr., Tampa, FL 33612, United States
SOURCE: Journal of Biological Chemistry, (27 Oct 2000) 275/43 (33981-33987).
Refs: 39
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB . . . A (TSA), a global repressor of histone deacetylase activity, inhibits the proliferation of a number of cell types. However, the **identification** of the mechanisms underlying TSA-mediated growth arrests has remained elusive. In order to resolve in more detail the cellular process **modulated** during the growth inhibition induced by TSA, we studied the effect of the drug on G0/G1 traverse in mitogen-stimulated quiescent Balb/c-3T3 cells. **Cyclin** D1 and retinoblastoma proteins were induced following the mitogenic stimulation of both control and TSA-treated cells, and **cyclin** D1 formed complexes with CDK4 under both conditions. However, **cyclin** D1-associated kinase was not increased in growth-arrested cells. The lack of **cyclin** D-associated kinase was paralleled by an accumulation of RB in a hypophosphorylated form, as would be expected. In contrast, p130. . . presence of E2F complexes not bound to pocket proteins, late G1 E2F-dependent gene expression was not observed. The lack of **cyclin** D1-associated kinase in TSA-treated cultures was potentially due to high levels of the **cyclin**-dependent inhibitor p27(kip1). However, the **modulation** of p27(kip1) levels by the deacetylase inhibitor cannot be responsible for the induction of the cell cycle arrest, since the growth of murine embryo fibroblasts deficient in both p27(kip1) and **p21**(cip1) was also inhibited by TSA. These data support a model in which TSA inhibits very early cell cycle traverse, which, in turn, leads to a decrease in **cyclin** D1-associated kinase activation and a repression of late cell cycle-dependent events. Alterations in early G0/G1 gene expression accompany the TSA-mediated. . .

L9 ANSWER 5 OF 37 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000217019 EMBASE
TITLE: Association between polymorphism in p21(Waf1/Cip1) cyclin-dependent kinase inhibitor gene and human oral cancer.
AUTHOR: Ralhan R.; Agarwal S.; Mathur M.; Wasylyk B.; Srivastava A.
CORPORATE SOURCE: R. Ralhan, Department of Biochemistry, All India Inst. of Medical Sciences, Ansari Nagar, New Delhi 110029, India. rralhan@medinst.ernet.in
SOURCE: Clinical Cancer Research, (2000) 6/6 (2440-2447).
Refs: 25
ISSN: 1078-0432 CODEN: CCREF4
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
LANGUAGE: English

SUMMARY LANGUAGE: English

AB The **cyclin**-dependent kinase inhibitor gene **p21** (Waf1/Cip1) plays a central role in inducing cellular growth arrest, terminal differentiation, and apoptosis. Alterations in this gene may adversely affect regulation of these processes and increase susceptibility for cancer. We have recently reported a novel polymorphism in the **p21**(Waf1/Cip1) gene in the Indian population and its association with esophageal cancer. An A.fwdarw.G transition at codon 149 resulted in amino acid substitution from aspartate to glycine in the proliferating cell nuclear antigen binding COOH-terminal domain of **p21** (Waf1/Cip1) that may affect PCNA-**p21**(Waf1/Cip1) interactions, thereby affecting regulation of cellular proliferation, and may increase susceptibility for development of cancer. In a parallel study in our laboratory, we searched for putative **p21**((Waf1/Cip1) mutations in oral premalignant and malignant lesions. No somatic mutation was detected in exon 2 of **p21**(Waf1/Cip1). Interestingly, a codon 149 polymorphism variant (A.fwdarw.G) was **identified** in 11 of 30 (37%) premalignant lesions (7 of 19 hyperplastic lesions and 4 of 11 dysplastic lesions) and 11 of 30 (37%) squamous cell carcinomas (SCCs). This codon 149 variant was also **identified** in paired lymphocytes of all of the patients with premalignant lesions and SCCs harboring the variant allele, suggesting the occurrence of a polymorphism. Lymphocyte DNA isolated from 50 unrelated age- and gender-matched healthy subjects was **screened** for this polymorphism. Seven of 50 (14%) normal controls harbored the A.fwdarw.G codon 149 variant allele. Immunohistochemical analysis of **p21**(Waf1/Cip1) protein expression showed immunoreactivity in 19 of these 30 (63%) oral premalignant lesions and 16 of 30 (53%) SCCs. The. . . also in patients with premalignant lesions (P = 0.038), compared with normal controls; and (b) the significantly higher frequency of **p21**(waf1/cip1) variants (codon 149) in oral premalignant lesions (10 of 11 cases) and SCCs (11 of 11 cases) with wild-type p53. . . suggesting that this polymorphism affects the p53 pathway and may play a vital role in oral tumorigenesis. Furthermore, overexpression of **p21** protein in oral lesions harboring missense mutations in the p53 gene suggest a p53-independent role for **p21** in the pathogenesis of oral cancer.

L9 ANSWER 6 OF 37 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2000394207 EMBASE

TITLE: Inhibitors of cyclin-dependent kinases as anti-cancer therapeutics.

AUTHOR: Fischer P.M.; Lane D.P.

CORPORATE SOURCE: P.M. Fischer, Cyclacel Limited, Dundee Technopole, James Lindsay Place, Dundee DD1 5JJ, United Kingdom. pfischer@cyclacel.com

SOURCE: Current Medicinal Chemistry, (2000) 7/12 (1213-1245). Refs: 148
ISSN: 0929-8673 CODEN: CMCHE7

COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Initiation, progression, and completion of the cell cycle are regulated by various **cyclin**-dependent kinases (CDKs), which are thus critical for cell growth. Tumour development is closely associated with genetic alteration and deregulation of. . . may be useful anti-cancer therapeutics. Indeed, early results suggest that transformed and normal cells differ in their requirement for e.g. **cyclin**/CDK2 and that it may be possible to develop novel antineoplastic agents devoid of the general host toxicity observed with conventional. . . active-site

inhibitors of CDKs have been studied; the main limitation with these ATP antagonists is kinase specificity for CDKs. However, **screening** of compound collections, as well as rational design based on enzyme-ligand complex crystal structures, are now yielding pre-clinical candidates, particularly. . . purine and flavonoid analogues, with impressive potency and selectivity. Natural CDK inhibitors (CKIs), e.g. the tumour suppressor gene products p16(INK4), **p21**(WAF1), and p27(KIP1), form the starting point for the design of mechanism-based CDK inhibitors. A number of these small proteins have been dissected and inhibitory lead peptides amenable to peptidomimetic development have been **identified**. Conversion of these peptides into pharmaceutically useful molecules is greatly aided by the recent elucidation of CKI/CDK crystal and solution. . . being exploited for the purposes of inhibitor design include: phosphorylation/dephosphorylation sites, macromolecular substrate binding site, CKS regulatory subunit binding sites, **cyclin**-binding site, cellular localisation domain, and destruction box. Finally, progress has recently been made in the application of antisense technology in. . .

L9 ANSWER 7 OF 37 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2001:20039 BIOSIS
DOCUMENT NUMBER: PREV200100020039
TITLE: Suberoylanilide hydroxamic acid as a potential therapeutic agent for human breast cancer treatment.
AUTHOR(S): Huang, Lili; Pardee, Arthur B. (1)
CORPORATE SOURCE: (1) Division of Cancer Biology, Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA, 02115: pardee@mbcrr.harvard.edu USA
SOURCE: Molecular Medicine (New York), (October, 2000) Vol. 6, No. 10, pp. 849-866. print.
ISSN: 1076-1551.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB. . . apoptosis analysis. The effects of SAHA on cell cycle and apoptosis regulatory proteins were examined by Western blots analysis. The **identification** of additional target genes was carried out by differential display (DD) and reverse transcription-polymerase chain reaction (RT-PCR). Results: SAHA inhibited. . . cell death, DNA laddering, and cleavage of poly(ADP-ribose) polymerase, indicating the involvement of caspases in SAHA-mediated apoptosis. In addition, SAHA **modulated** cell cycle and apoptosis regulatory proteins. For example, **cyclin**-dependent kinase (CDK) inhibitors p21WAF1/Cip1 and p27Kip1 were induced, and retinoblastoma protein pRb was hypophosphorylated. Moreover, SAHA induced several genes associated. . . genes encode gelsolin, isopentenyl-diphosphate delta isomerase (IDI1), and 1,25-dihydroxyvitamin D-3 up-regulated protein 1 (VDUP1), the last two of which were **identified** by DD. Induction of these genes may contribute to SAHA-mediated pro-differentiating and antiproliferative effects. Conclusions: SAHA induced growth inhibition, cell cycle arrest, and eventual apoptosis in human breast cancer cells, possibly by **modulating** cell cycle and apoptosis regulatory proteins, such as CDK inhibitors **p21** and p27, pRb, and other differentiation and/or growth inhibition-associated genes, including gelsolin, IDI1 and VDUP1. This, together with the low. . .

L9 ANSWER 8 OF 37 MEDLINE
ACCESSION NUMBER: 2000417258 MEDLINE
DOCUMENT NUMBER: 20400842
TITLE: Anticarcinogenic effect of a polyphenolic fraction isolated from grape seeds in human prostate carcinoma DU145 cells:

modulation of mitogenic signaling and cell-cycle regulators
and induction of G1 arrest and apoptosis.
AUTHOR: Agarwal C; Sharma Y; Agarwal R
CORPORATE SOURCE: Center for Cancer Causation and Prevention, AMC Cancer Research Center, Denver, Colorado 80214, USA.
CONTRACT NUMBER: CA 64514 (NCI)
CA 83741 (NCI)
SOURCE: MOLECULAR CARCINOGENESIS, (2000 Jul) 28 (3) 129-38.
Journal code: AEQ. ISSN: 0899-1987.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 200011
ENTRY WEEK: 20001102
AB There is an increasing interest in **identifying** potent cancer preventive and therapeutic agents against prostate cancer (PCA). In a recent study, we showed that a polyphenolic fraction. . . (P < 0.1-0.001) in phospho-ERK2 levels, respectively. In other studies, similar
doses of GSP showed up to 1.9-fold increases in Cip1/**p21** and a significant (P < 0.001) decrease in **cyclin**-dependent kinase (CDK) 4 (up to 90% decrease), CDK2 (up to 50% decrease), and **cyclin** E (up to 60% decrease). GSP treatment of DU145 cells also resulted in a significant (P < 0.001) G1 arrest. . . LNCaP. Together, these results suggest that GSP may exert strong anticarcinogenic effect against PCA and that this effect possibly involves **modulation** of mitogenic signaling and cell-cycle regulators and induction of G1 arrest, cell-growth inhibition, and apoptotic death. Mol. Carcinog. 28:129-138, 2000.. . .

L9 ANSWER 9 OF 37 MEDLINE
ACCESSION NUMBER: 2000020296 MEDLINE
DOCUMENT NUMBER: 20020296
TITLE: The protein SET regulates the inhibitory effect of p21(Cip1) on cyclin E-cyclin-dependent kinase 2 activity.
AUTHOR: Estanyol J M; Jaumot M; Casanovas O; Rodriguez-Vilarrupla A; Agell N; Bachs O
CORPORATE SOURCE: Departament de Biologia Cellular i Anatomia Patol`ogica, Facultat de Medicina, Institut d'Investigacions Biom`ediques August Pi Sunyer, Universitat de Barcelona, 08036 Barcelona, Spain.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Nov 12) 274 (46) 33161-5.
Journal code: HIV. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 200003
ENTRY WEEK: 20000302
AB The **cyclin**-dependent kinase (CDK) inhibitor **p21**(Cip1) has a dual role in the regulation of the cell cycle; it is an activator of
cyclin D1-CDK4 complexes and an inhibitor of **cyclins** E/A-CDK2 activity. By affinity chromatography with **p21** (Cip1)-Sepharose 4B columns, we purified a 39-kDa protein, which was **identified** by microsequence analysis as the oncoprotein SET. Complexes containing SET and **p21**(Cip1) were detected in vivo by immunoprecipitation of Namalwa cell extracts using specific anti-**p21**(Cip1) antibodies. We found that SET bound directly to **p21**(Cip1) in vitro by the carboxyl-terminal region of **p21** (Cip1). SET had no direct effect on **cyclin** E/A-CDK2 activity, although it reversed the inhibition of **cyclin** E-CDK2, but not of **cyclin** A-CDK2, induced by **p21**(Cip1). This result is

specific for **p21**(Cip1), since SET neither bound to p27(Kip1) nor reversed its inhibitory effect on **cyclin** E-CDK2 or **cyclin** A-CDK2. Thus, SET appears to be a **modulator** of **p21**(Cip1) inhibitory function. These results suggest that SET can regulate G(1)/S transition by **modulating** the activity of **cyclin** E-CDK2.

L9 ANSWER 10 OF 37 MEDLINE
ACCESSION NUMBER: 1999290651 MEDLINE
DOCUMENT NUMBER: 99290651
TITLE: Proteasome inhibitors: a novel class of potent and effective antitumor agents.
AUTHOR: Adams J; Palombella V J; Sausville E A; Johnson J; Destree A; Lazarus D D; Maas J; Pien C S; Prakash S; Elliott P J
CORPORATE SOURCE: ProScript, Inc., Cambridge, Massachusetts 02139, USA.. jadams@proscript.com
SOURCE: CANCER RESEARCH, (1999 Jun 1) 59 (11) 2615-22. Journal code: CNF. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199909
ENTRY WEEK: 19990901
AB . . . series of proteasome inhibitors, exemplified by PS-341, which we describe here. As determined by the National Cancer Institute in vitro **screen**, PS-341 has substantial cytotoxicity against a broad range of human tumor cells, including prostate cancer cell lines. The PC-3 prostate. . . PS-341. In vitro, PS-341 elicits proteasome inhibition, leading to an increase in the intracellular levels of specific proteins, including the **cyclin**-dependent kinase inhibitor, **p21**. Moreover, exposure of such cells to PS-341 caused them to accumulate in the G2-M phase of the cell cycle and. . . Studies also revealed that i.v. administration of PS-341 resulted in a rapid and widespread distribution of PS-341, with highest levels **identified** in the liver and gastrointestinal tract and lowest levels in the skin and muscle.
Modest levels were found in the. . .

L9 ANSWER 11 OF 37 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:143120 CAPLUS
DOCUMENT NUMBER: 133:72019
TITLE: p53 tumor suppressor gene: its role in DNA damage response and cancer
AUTHOR(S): Ozturk, Mehmet; Unsal, Kezban
CORPORATE SOURCE: Department of Molecular Biology and Genetics, Bilkent University, Bilkent, 06533, Turk.
SOURCE: NATO ASI Ser., Ser. A (1999), 302(Advances in DNA Damage and Repair), 371-376
CODEN: NALSDJ; ISSN: 0258-1213
PUBLISHER: Kluwer Academic/Plenum Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
REFERENCE COUNT: 21
REFERENCE(S): (1) Band, V; EMBO J 1993, V12, P1847 CAPLUS
(2) Chen, C; Proc Natl Acad Sci USA 1994, V91, P2684 CAPLUS
(3) El-Deiry, W; Nat Genet 1992, V1, P45 CAPLUS
(4) Feitelson, M; Oncogene 1993, V8, P1109 CAPLUS
(5) Jenkins, J; Nucl Acids Res 1984, V12, P5609
CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB A review, with 21 refs. P53 is one of the tumor suppressor genes mutated in great majority of human cancers. The protein product of p53 gene is a nuclear phosphoprotein with characteristic features of a transcription factor acting on different target genes to **modulate** their

expression either pos. or neg. Normal cellular functions of p53 are closely related to DNA damage response inducible by a variety of agents. Upon DNA damage, p53 protein is 'activated' by an unknown mechanism. P53 activation is accompanied by an increased half life and nuclear accumulation. This is followed by a change of expression of different genes some of which are directly related to cell cycle arrest and apoptosis. The main, cell-cycle-regulatory target of p53 is **p21** , a member of **cyclin**-dependent kinase inhibitory proteins. P53-mediated induction of **p21** expression leads to a cell-cycle arrest at the G1 phase of the cycle. Another target of p53 is bax, a protein well-known for its activator role of apoptosis. A new family of p53 target genes have been recently **identified**. Their protein products may be involved in the oxidative state of cells. Some of the apoptotic activities of p53 may be mediated by these newly **identified** genes. Finally, a new gene encoding a close homolog of p53 protein has been **identified**. This relative of p53, named p73 shares strong homol. with p53 at the DNA binding and transactivation domains. In addn., p73 has extra carboxy-terminal sequences with no homol. to known proteins. P73 appears to be insensitive to DNA damage, but it probably acts on known p53 target genes with equal efficiency. It remains to be detd. whether p73 is also a tumor suppressor gene mutated in cancer cells.

L9 ANSWER 12 OF 37 MEDLINE
ACCESSION NUMBER: 1999403006 MEDLINE
DOCUMENT NUMBER: 99403006
TITLE: A genetic screen for modifiers of E2F in Drosophila melanogaster.
AUTHOR: Staehling-Hampton K; Ciampa P J; Brook A; Dyson N
CORPORATE SOURCE: Massachusetts General Hospital Cancer Center, Charlestown, Massachusetts 02129, USA.
CONTRACT NUMBER: GM-53203 (NIGMS)
SOURCE: GENETICS, (1999 Sep) 153 (1) 275-87.
Journal code: FNH. ISSN: 0016-6731.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY WEEK: 20000104
AB . . . in part by pRB, the protein product of the retinoblastoma tumor suppressor gene. Studies of tumor cells show that the p16(ink4a)/cdk4/ **cyclin** D/pRB pathway is mutated in most forms of cancer, suggesting that the deregulation of E2F, and hence the cell cycle,. . . cell-cycle control and may play a role in tumorigenesis. We used an E2F overexpression phenotype in the Drosophila eye to **screen** for modifiers of E2F activity. Coexpression of dE2F and its heterodimeric partner dDP in the fly eye induces S phases and cell death. We isolated 33 enhancer mutations of this phenotype by EMS and X-ray mutagenesis and by **screening** a deficiency library collection. The majority of these mutations sorted into six complementation groups, five of which have been **identified** as alleles of brahma (brm), moira (mor) osa, pointed (pnt), and polycephalon (poc). osa, brm, and mor encode proteins with. . . of a SWI/SNF chromatin-remodeling complex has an important impact on E2F-dependent phenotypes. Mutations in poc also suppress phenotypes caused by **p21**(CIP1) expression, indicating an important role for polycephalon in cell-cycle control.

L9 ANSWER 13 OF 37 MEDLINE
ACCESSION NUMBER: 1999208479 MEDLINE
DOCUMENT NUMBER: 99208479
TITLE: The mechanisms of death of an erythroleukemic cell line by p53: involvement of the microtubule and mitochondria.

AUTHOR: Kato M V
CORPORATE SOURCE: Molecular Oncology Laboratory, Tsukuba Life Science Center,
The Institute of Physical and Chemical Research (RIKEN), Ibaraki, Japan.. mkato@rtc.riken.go.jp
SOURCE: LEUKEMIA AND LYMPHOMA, (1999 Mar) 33 (1-2) 181-6.
Journal code: BNQ. ISSN: 1042-8194.
PUB. COUNTRY: Switzerland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908

AB . . . were cultured at 32 degrees C. In this process, p53 recovered the wild-type p53 function and the expression of the **p21** (waf1/cip1/sdi1), **cyclin** G1 and gadd45 genes was increased. However, no significant changes were detected in the expression of the mdm2, bcl-2, bax, fas and fasl genes, suggesting the existence of other genes associated with apoptosis. Genes up-regulated by p53 were **screened** by the mRNA differential display method. One of the up-regulated genes was **identified** as the elongation factor 1 alpha (EF-1 alpha) gene. EF-1 alpha is also a microtubule-severing protein. Upon the temperature-shift, the. . . of EF-1 alpha by p53 may be a cause of the cell death. On the other hand, the function of **cyclin** G1 is not so clear despite the fact that 1-2-3 cells showed a significant increase of the **cyclin** G1 gene during the early stage of apoptosis. The yeast two-hybrid system was used to **identify cyclin** G1-associated proteins. One is a cytochrome c (Cyt c) oxidase subunit II (COXII). **Cyclin** G1 and COXII were co-immunoprecipitated from an extract of human osteosarcoma cell line that expressed high levels of **cyclin** G1. COX activity was also increased by temperature-shift in this cell line. The pattern of changes in COX activity was closely reflected by the expression of the **cyclin** G1 gene. **Cyclin** G1 and COXII associate physically with each other in vivo and that activation of COXII by binding to **cyclin** G1 upregulated by p53 may be associated with apoptosis. These two new pathways, p53-EF-1 alpha-microtubule-severing (-distortion of cytoskeleton) and p53-**cyclin** G1-COXII (-CytC, ATP-caspase-3 activation), may cooperate to induce apoptosis in this cell line.

L9 ANSWER 14 OF 37 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:550494 CAPLUS
DOCUMENT NUMBER: 129:172777
TITLE: P21CIP1 or p27KIP1 effects on the regulation of differentiation of human mesenchymal stem cells
INVENTOR(S): Connolly, Timothy J.
PATENT ASSIGNEE(S): Osiris Therapeutics, Inc., USA
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9835022	A1	19980813	WO 1998-US2137	19980205
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9861444	A1	19980826	AU 1998-61444	19980205
PRIORITY APPLN. INFO.:			US 1997-36917	19970206
			WO 1998-US2137	19980205

AB Disclosed is a method for distinguishing undifferentiated human mesenchymal stem cells (hMSCs) from partially or completely differentiated

human mesenchymal cells. In accordance with the invention it has been discovered that the expression of **p21 Cyclin** Inhibitor Protein (p21CIP1) is upregulated in partially or completely differentiated human mesenchymal cells as compared to undifferentiated hMSCs. Thus, this provides a quality control marker and test or assay to confirm that hMSCs are truly undifferentiated. That the p21CIP1 gene is either not expressed in clearly undifferentiated hMSCs or is significantly upregulated in partially or completely differentiated human mesenchymal cells by mesenchymal lineage inducers provides a **screening** method for **identifying** previously unknown mesenchymal lineage inducers. Also disclosed is an assay to det. the competence of mesenchymal progenitor cells to differentiate, particularly for in vivo tissue repair and particularly with respect to the osteogenic lineage. The inventors have made this possible by their observation that, in cells at approx. 80% confluence in in vitro culture, p27 Kinase Inhibitor Protein (p27KIP1) expression levels are upregulated in differentiation competent mesenchymal stem cell as compared to differentiation incompetent mesenchymal stem cells.

L9 ANSWER 15 OF 37 USPATFULL

ACCESSION NUMBER:	1998:58092 USPATFULL
TITLE:	CDC37 cell-cycle regulatory protein, and uses related thereto
INVENTOR(S):	Gyuris, Jeno, Winchester, MA, United States Lamphere, Lou, Boston, MA, United States Draetta, Giulio, Milan, Italy
PATENT ASSIGNEE(S):	Mitotix, Inc., Cambridge, MA, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5756671	19980526
APPLICATION INFO.:	US 1996-625209	19960401 (8)

RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1995-466679, filed on 6 Jun 1995, now abandoned which is a continuation-in-part of Ser. No. US 1994-253155, filed on 2 Jun 1994, now patented, Pat. No. US 5691147
DOCUMENT TYPE:	Utility
PRIMARY EXAMINER:	Walsh, Stephen
ASSISTANT EXAMINER:	Sorensen, Kenneth A.
LEGAL REPRESENTATIVE:	Foley, Hoag & Eliot LLP; Vincent, Esq., Matthew P.; Arnold, Esq., Beth E.
NUMBER OF CLAIMS:	37
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	1 Drawing Figure(s); 1 Drawing Page(s)
LINE COUNT:	2687

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . the appended examples and in parent application U.S. Ser. No. 08/253,155, a CDK4-dependent interaction trap assay (ITS) was used to **identify** proteins that can associate with human CDK4. The present invention, as set out below, derives from the discovery that, in addition to **cyclins**, **p21**, p16, and PCNA, CDK4 is also associated with several other cellular proteins (hereinafter termed "CDK4-binding proteins" or "CDK4-BPs"), which associations. . . control various aspects of the kinases's activity, including both catalytic activity and substrate specificity. Thus, because each of the proteins **identified** by the subject ITS act close to the point of CDK4 process control, such as by channeling converging upstream signals. . . activity by directing divergent downstream signal propagation from CDK4, each protein is a potential therapeutic target

for agents capable of **modulating** cell proliferation and/or differentiation.

L9 ANSWER 16 OF 37 USPATFULL
ACCESSION NUMBER: 1998:36530 USPATFULL
TITLE: Method and kit for evaluating human papillomavirus transformed cells
INVENTOR(S): Munger, Karl, Brookline, MA, United States
Jones, D. Leanne, Somerville, MA, United States
PATENT ASSIGNEE(S): President and Fellows of Harvard College, Cambridge, MA, United States (U.S. corporation)
Harvard University, Office of Technology Transfer, Cambridge, MA, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5736318	19980407
APPLICATION INFO.:	US 1995-406248	19950317 (8)

DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Knode, Marian C.
ASSISTANT EXAMINER: Salimi, Ali R.
LEGAL REPRESENTATIVE: Hale and Dorr LLP
NUMBER OF CLAIMS: 1
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 789
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . p53 stimulates expression of a number of genes, for example, the gene encoding a 21 kD protein variously known as **p21**, WAF1, SDI1, PIC1 and CIP1 (hereinafter referred to as **p21** .sup.CIP1). The nucleotide and amino acid sequences of **p21** .sup.CIP1 are set forth in SEQ ID NO:1 and SEQ ID NO:2. The **p21** .sup.CIP1 protein suppresses growth by inhibiting the activities of a class of protein kinases, the **cyclin** dependent kinases (cdks), which affect the temporal progression of the cell cycle. In their native state, the cdks form complexes with a regulatory subunit (a **cyclin**). A large number of **cyclins** have been **identified**, as have the specific cdks with which they associate. See, for example, PCT/US/00961 and T. Hunter et al., Cell 79, 573-582 (1994), incorporated herein by reference. When the **cyclin**/cdk complexes are inhibited by **p21**.sup.CIP1, cell division is blocked at an important checkpoint in the late G1 phase early in the cell replication cycle. When **p21**.sup.CIP1 does not inhibit the **cyclin**/cdk complexes, they stimulate cells to proceed through the cell cycle by phosphorylating and thus **modulating** the activity of the RB tumor suppressor as well as other regulatory proteins.

L9 ANSWER 17 OF 37 MEDLINE
ACCESSION NUMBER: 1998240990 MEDLINE
DOCUMENT NUMBER: 98240990
TITLE: A flavonoid antioxidant, silymarin, inhibits activation of erbB1 signaling and induces cyclin-dependent kinase inhibitors, G1 arrest, and anticarcinogenic effects in human prostate carcinoma DU145 cells.
AUTHOR: Zi X; Grasso A W; Kung H J; Agarwal R
CORPORATE SOURCE: Department of Dermatology, Case Western Reserve University, Cleveland, Ohio 44106, USA.
CONTRACT NUMBER: CA 64514 (NCI)
P30-CA 43703 (NCI)
SOURCE: CANCER RESEARCH, (1998 May 1) 58 (9) 1920-9.
Journal code: CNF. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199808
AB . . . members of the erbB family have been shown to play important roles in human PCA, efforts should be directed to **identify** inhibitors of this pathway for PCA intervention. In this study, we assessed whether silymarin inhibits erbB1 activation and associated downstream events and **modulates** cell cycle regulatory proteins and progression, leading to growth inhibition of human prostate carcinoma DU145 cells. Treatment of serum-starved cells. . . erbB1. In the studies analyzing cell cycle regulatory molecules, silymarin treatment of cells also resulted in a significant induction of **cyclin** -dependent kinase inhibitors (CDKIs) Cip1/**p21** and Kip1/p27, concomitant with a significant decrease in CDK4 expression, but no change in the levels of CDK2 and CDK6 and their associated **cyclins** E and D1, respectively. Cells treated with silymarin also showed an increased binding of CDKIs with CDKs, together with a marked decrease in the kinase activity of CDKs and associated **cyclins**. In additional studies, treatment of cells grown in 10% serum with anti-epidermal growth factor receptor monoclonal antibody clone 225 or.

. change in their protein levels. Furthermore, whereas silymarin treatment resulted in a significant increase in the protein levels of both Cip1/**p21** and Kip1/p27, monoclonal antibody 225 showed an increase only in Kip1/p27. These findings suggest that silymarin also inhibits constitutive activation. . . case of Kip1/p27; however, additional pathways independent of inhibition of erbB1 activation are possibly responsible for the silymarin-caused increase in Cip1/**p21** in DU145 cells. In other studies, silymarin treatment also induced a G1 arrest in the cell cycle progression of DU145. . .

L9 ANSWER 18 OF 37 MEDLINE
ACCESSION NUMBER: 1999003537 MEDLINE
DOCUMENT NUMBER: 99003537
TITLE: The p16(INK4A) protein and flavopiridol restore yeast cell growth inhibited by Cdk4.
AUTHOR: Moorthamer M; Panchal M; Greenhalf W; Chaudhuri B
CORPORATE SOURCE: Oncology Research, Novartis Pharma AG, Basel, Switzerland.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1998 Sep 29) 250 (3) 791-7.
Journal code: 9Y8. ISSN: 0006-291X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199901
ENTRY WEEK: 19990104
AB **Cyclin**-dependent kinase 4 (Cdk4) activity is misregulated in most cancers. Loss of Cdk4 regulation can occur through overexpression of Cdk4 catalytic subunit or its regulatory partner **cyclin** D1, or if the Cdk4-specific inhibitory protein p16(INK4A) is inactive. We have attempted to express the two human subunits, Cdk4 and **cyclin** D1, in the yeast Saccharomyces cerevisiae. Surprisingly, expression of Cdk4 alone, under control of the strong GAL promoter, inhibits cell growth. Coexpression of both subunits allows formation of an active Cdk4-**cyclin** D1 complex which accentuates growth arrest. In cells expressing Cdk4 only, growth is restored by overexpressing human Cdc37, a Cdk4-binding molecular chaperone. Interestingly, the effect of Cdk4 on yeast is also overcome by both p16- and **p21**-families of Cdk-inhibitory proteins. Moreover, flavopiridol, a compound which inhibits Cdk4 enzyme activity, restores cell division. The fact that p16(INK4A) and flavopiridol negate Cdk4-mediated suppression of yeast cell growth implies

that this simple system can be used as a **screen** for **identifying** Cdk4-specific antagonists which may mimic p16(INK4A) in the cancer cell cycle. Copyright 1998 Academic Press.

L9 ANSWER 19 OF 37 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999026807 EMBASE
TITLE: Alterations in cyclin-dependent kinase 2 function during differentiation of primary human keratinocytes.
AUTHOR: Alani R.M.; Hasskarl J.; Munger K.
CORPORATE SOURCE: K. Munger, Pathology Department, Harvard Center for Cancer Biology, Harvard Medical School, 200 Longwood Avenue, Boston, MA 02115-5701, United States
SOURCE: Molecular Carcinogenesis, (1998) 23/4 (226-233).
Refs: 71
ISSN: 0899-1987 CODEN: MOCAE8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
LANGUAGE: English
SUMMARY LANGUAGE: English
AB . . . these two processes is critical to maintenance of epidermal tissue homeostasis and is frequently disrupted in squamous cell carcinoma.
To **identify** possible molecular targets of epithelial carcinogenesis, we investigated the regulatory pathways that couple cellular differentiation and proliferation in primary cultures of human keratinocytes and found that the **cyclin**-dependent kinase inhibitors (CKIs) **p21**(cip1/waf1) and p27(kip1) were induced early during differentiation of human keratinocytes, whereas p15(ink4B) was induced later in differentiation. The induction of **p21** (cip1/waf1) was mediated by both transcriptional and non- transcriptional mechanisms, and the activities of **cyclin** A/**cyclin** -dependent kinase (cdk) 2 and **cyclin** E/cdk2 complexes were specifically inhibited during keratinocyte differentiation. In contrast, **p21**(cip1/waf1) did not associate with cdk4, and the activities of cdk4 complexes remained unchanged. Hence, our results support the model that multiple CKIs participate in linking cellular proliferation and differentiation in human keratinocytes by specific **modulation** of cdk2 activity.

L9 ANSWER 20 OF 37 MEDLINE
ACCESSION NUMBER: 1999107110 MEDLINE
DOCUMENT NUMBER: 99107110
TITLE: Analysis of the p21 gene in gliomas.
AUTHOR: Li Y J; Hoang-Xuan K; Zhou X P; Sanson M; Mokhtari K; Faillot T; Cornu P; Poisson M; Thomas G; Hamelin R
CORPORATE SOURCE: INSERM U434, Genetique des Tumeurs, CEPH, Paris, France.
SOURCE: JOURNAL OF NEURO-ONCOLOGY, (1998 Nov) 40 (2) 107-11.
Journal code: JCP. ISSN: 0167-594X.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
AB The **p21** gene encodes a **cyclin** dependent kinase inhibitor protein (**p21**) which has a tumor suppressive activity in a variety of tumor cell lines. Since, the **p21** gene is up-regulated by the p53 tumor suppressor gene, which is frequently mutated in gliomas, acting therefore in the same. . . gliomas (48 glioblastomas, 11 anaplastic astrocytomas, 10 low-grade astrocytomas, 12 oligodendrogliomas and mixed gliomas), were investigated for mutations in the **p21** coding sequence by denaturant gradient gel electrophoresis followed by sequencing. All these tumors have been previously **screened** for p53 mutations. Three different DNA variants were **identified** on codon 31 (17 cases), 27 (1 case) and

117 (1 case) and shown to be also present in matching. . . . suggesting they were polymorphisms. None of the tumors demonstrated a somatic mutation. No significant correlation between the presence of a **p21** variant and the p53 mutation tumor status was observed. In conclusion, mutation in the **p21** gene unlikely contributes to the development of gliomas.

L9 ANSWER 21 OF 37 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:746076 CAPLUS
DOCUMENT NUMBER: 128:18686
TITLE: Methods and means using p21WAF1 peptide fragments for inhibition of cdk4 activity
INVENTOR(S): Ball, Kathryn Lindsay; Lane, David Philip
PATENT ASSIGNEE(S): Cyclacel Limited, UK; Ball, Kathryn Lindsay; Lane, David Philip
SOURCE: PCT Int. Appl., 105 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9742222	A1	19971113	WO 1997-GB1250	19970508
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9727077	A1	19971126	AU 1997-27077	19970508
EP 898580	A1	19990303	EP 1997-920857	19970508
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2000513805	T2	20001017	JP 1997-529635	19970508
PRIORITY APPLN. INFO.:			GB 1996-9521	19960508
			GB 1996-21314	19961009
			WO 1997-GB1250	19970508

OTHER SOURCE(S): MARPAT 128:18686
AB P21WAF1 interacts with **cyclin** D1 and Cdk4. Peptide fragments of **p21** inhibit the interaction and/or affect Cdk4 activity. The peptides, deriv. peptides, and nonpeptidyl mimetics thereof are useful in affecting activity of Cdk4, such as RB phosphorylation, and cellular proliferation, indicative of therapeutic usefulness in treatment of tumors
and other hyperproliferative disorders. Assay and **screening** methods allow **identification** of such **modulators**, esp. inhibitors, of Cdk4 activity.

L9 ANSWER 22 OF 37 MEDLINE
ACCESSION NUMBER: 97334867 MEDLINE
DOCUMENT NUMBER: 97334867
TITLE: Association between human cancer and two polymorphisms occurring together in the p21Waf1/Cip1 cyclin-dependent kinase inhibitor gene.
AUTHOR: Facher E A; Becich M J; Deka A; Law J C
CORPORATE SOURCE: Department of Human Genetics, University of Pittsburgh, PA 15261, USA.
SOURCE: CANCER, (1997 Jun 15) 79 (12) 2424-9.
Journal code: CLZ. ISSN: 0008-543X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199708
ENTRY WEEK: 19970804
AB BACKGROUND: The **cyclin**-dependent kinase inhibitor gene p21Waf1/Cip1 plays a role in signaling cellular growth arrest. In response to DNA damage, **p21** is induced by the p53 gene, thereby playing a direct role in mediating p53-induced G1 arrest. Alterations in this gene. . . may adversely affect regulation of cellular proliferation and increase susceptibility for cancer. Two polymorphisms have previously been characterized in the **p21** gene: a C-->A transversion at codon 31 (ser-->arg) and a C-->T transition 20 nucleotides downstream from the 3' end of exon 3. METHODS: The codon 31 polymorphism in exon 2 of the **p21** gene was **identified** by restriction digestion (Alw26I) of products amplified by polymerase chain reaction (PCR). The polymorphism downstream from exon 3 of the **p21** gene was **identified** by single strand conformation polymorphism (SSCP) analysis of PCR amplified products and was confirmed by PstI enzyme restriction digestion. DNA. . . alleles were confirmed by direct DNA sequencing. The entire coding region and the promoter region (p53 binding domain) of the **p21** gene were **screened** for mutations by SSCP analysis or DNA sequencing. RESULTS: The two polymorphisms were found in 18 of 96 tumor samples lacking p53 alterations (18.8%). Nine of 54 prostate adenocarcinoma samples (16.7%) contained both **p21** variants, whereas 9 of 42 squamous cell carcinomas of the head and neck (21.4%) displayed both polymorphisms. Of the 110 controls examined, 10 (9.1%) had both alterations. Both **p21** polymorphisms occurred together in all samples examined and there was no indication of mutation in the coding region of the **p21** gene or in the p53 binding domain of the promoter region. CONCLUSIONS: These data suggest that **p21** gene variants may play a role in increased susceptibility for the development of some types of cancer. In the current. . .

L9 ANSWER 23 OF 37 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:27712 BIOSIS
DOCUMENT NUMBER: PREV199800027712
TITLE: Interaction of the cyclin-dependent kinase inhibitor p21 with PCNA: A link between cell cycle and DNA repair.
AUTHOR(S): Cayrol, Corinne; Ducommun, Bernard (1)
CORPORATE SOURCE: (1) Inst. Pharmacol. Biol. Structurale CNRS, UPR 9062, Univ. Paul-Sabatier, 205 route de Narbonne, 31077 Toulouse Cedex France
SOURCE: M-S (Medecine Sciences), (Nov., 1997) Vol. 13, No. 11, pp. 1259-1265.
ISSN: 0767-0974.
DOCUMENT TYPE: General Review
LANGUAGE: French
SUMMARY LANGUAGE: French; English
AB The **cyclin**-dependent kinase (CDK) inhibitors, or CKIs, play an essential role in the control of cell proliferation. CKIs regulate G1/S progression through the **modulation** of **cyclin**/CDK complexes activity in response to various intracellular or extracellular signals. p21Cip1, the first CKI **identified**, plays a key role in growth arrest induced by the tumor suppressor p53 in response to DNA damage. A unique feature of **p21** that distinguishes it from other CKIs is its ability to associate with the proliferating cell nuclear antigen (PCNA), an auxiliary. . . delta and epsilon, that is essential for both DNA replication and DNA repair. The association, in non-transformed human cells of **p21** with PCNA and various **cyclin**/CDKs in **p21**/PCNA/**cyclin**/CDK quaternary complexes provides an important link between the cell cycle, DNA replication and DNA repair. **p21** contains a C-terminal PCNA binding motif that interacts with the interdomain connector loop of PCNA

and inhibits PCNA-dependent DNA replication. . . might inhibit cell cycle progression independently of the N-terminal CDK inhibitory domain and thus contribute to the antiproliferative activity of **p21**. In contrast to its inhibitory effect on DNA replication and mismatch repair, **p21** does not appear to block PCNA-dependent nucleotide excision repair. Therefore, **p21** induction after DNA damage may lead to inhibition of cell cycle progression and inactivation of PCNA-dependent DNA replication, while permitting. . .

L9 ANSWER 24 OF 37 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:261391 BIOSIS
DOCUMENT NUMBER: PREV199799567994
TITLE: Current concepts in neuro-oncology: The cell cycle: A review.
AUTHOR(S): Dirks, Peter B.; Rutka, James T.
CORPORATE SOURCE: Div. Neurosurg., Suite 1504, The Hosp. Sick Children,, 555 University Ave., Toronto, Ontario M5G 1X8 Canada
SOURCE: Neurosurgery (Baltimore), (1997) Vol. 40, No. 5, pp. 1000-1015.
ISSN: 0148-396X.
DOCUMENT TYPE: General Review
LANGUAGE: English
AB. . . and balances of the normal cell cycle. Recently, a number of major advances in molecular biology have led to the **identification** of several critical genetic and enzymatic pathways that are disturbed in cancer cells resulting in uncontrolled cell cycling. We now. . . in part by a series of protein kinases, the activity of which is regulated by a group of proteins called **cyclins**. **Cyclins** act in concert with the **cyclin**-dependent kinases (CDKs) to phosphorylate key substrates that facilitate the passage of the cell through each phase of the cell cycle. A critical target of **cyclin** -CDK enzymes is the retinoblastoma tumor suppressor protein, and phosphorylation of this protein inhibits its ability to restrain activity of a family of transcription factors (E2F family), which induce expression of genes important for cell proliferation. In addition to the **cyclins** and CDKs, there is an emerging family of CDK inhibitors, which **modulate** the activity of **cyclins** and CDKs. CDK inhibitors inhibit **cyclin** cntdot CDK complexes and transduce internal or external growth-suppressive signals, which act on the cell cycle machinery. Accordingly, all CDK. . . feature of cancer cells is the abrogation of cell cycle checkpoints, either by aberrant expression of positive regulators (for example, **cyclins** and CDKs) or the loss of negative regulators, including **p21**-Cip1 through loss of function of its transcriptional activator p53, or deletion or mutation of p16-INK4A (multiple tumor suppressor 1/CDKN2) and. . .

L9 ANSWER 25 OF 37 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:261680 CAPLUS
DOCUMENT NUMBER: 129:77934
TITLE: Two-hybrid screening and the cell cycle
AUTHOR(S): Hannon, Gregory J.
CORPORATE SOURCE: Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 11724, USA
SOURCE: Yeast Two-Hybrid Syst. (1997), 183-196. Editor(s): Bartel, Paul L.; Fields, Stanley. Oxford University Press: New York, N. Y.
CODEN: 65YDA2
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review with 61 refs. The two-hybrid **screen** has been most often successful in the **identification** of stable, protein-protein interactions. Perhaps, because such interactions are

prevalent among components of cell cycle control, cell cycle regulatory proteins have proven amenable to the two-hybrid approach. Here, the authors discusses three aspects of cell cycle control in which the two-hybrid technique has been of particular importance. These are the regulation of the G1/S transition by phosphorylation of pRb, global control of cell cycle progression by the **p21**/p27 family of **cyclin**-dependent kinase (CDK) inhibitors and the role of CDK-activating kinase (CAK) and KAP in the metab. of threonine ~160 phosphorylation.

L9 ANSWER 26 OF 37 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:75244 BIOSIS
DOCUMENT NUMBER: PREV199799381947
TITLE: WAF1/Cip1 gene polymorphism and expression in carcinomas of the breast, ovary, and endometrium.
AUTHOR(S): Lukas, Jason; Groshen, Susan; Saffari, Bahman; Niu, Ning; Reles, Angela; Wen, Wen-Hsiang; Felix, Juan; Jones, Lovell A.; Hall, Frederick L.; Press, Michael F. (1)
CORPORATE SOURCE: (1) Dep. Pathol. Norris Cancer Cent., Mailslot 73, U.S.C. Sch. Med., 1441 Eastlake Ave., Los Angeles, CA 90033 USA
SOURCE: American Journal of Pathology, (1997) Vol. 150, No. 1, pp. 167-175.
ISSN: 0002-9440.
DOCUMENT TYPE: Article
LANGUAGE: English
AB. . . are potential sites for somatic alterations. WAF1/Cip1, also known as WAF1, Cip1, sdi1, or CAP20, codes for a 21-kd protein (**p21**-WAF1/Cip1), which was recently described as a universal inhibitor of **cyclins** and is thus critical in cell cycle control. Mutations in WAF1/Cip1 are potentially important in human malignancies because they could affect the control of the cell cycle. To understand whether mutations of WAF1/Cip1 occur in cancer, we **screened** 53 cases of invasive breast carcinoma, 35 cases of ductal carcinoma in situ (DCIS), 53 ovarian carcinomas-. and 47 endometrial carcinomas in the second exon of WAF1/Cip1 (90% of the open reading frame). **p21**-WAF1/Cip1 expression was characterized with immunohistochemistry. Cells from the blood of 21 normal individuals were also characterized using single-strand conformational polymorphism. . . DCIS of the breast (14%), 8 invasive ovarian carcinomas (15%), and 9 endometrial carcinomas (19%). In total, 209 samples were **screened**, and 38 cases (18.2%) had an altered codon 31. Each case with altered single-strand conformational polymorphism, analyzed by DNA sequencing. . . These results indicate that codon 31 is a polymorphic site and that the serine to arginine shift is a polymorphism. **p21**-WAF1/Cip1 expression, **identified** by immunohistochemistry, was found to vary in a pattern that depended both on the tissue type and on the presence. . .

L9 ANSWER 27 OF 37 MEDLINE
ACCESSION NUMBER: 97193881 MEDLINE
DOCUMENT NUMBER: 97193881
TITLE: A role for the cyclin-dependent kinase inhibitor p21 in the G1 cell cycle arrest mediated by the type I interferons [published erratum appears in J Interferon Cytokine Res 1997 May;17(5):318].
AUTHOR: Subramaniam P S; Johnson H M
CORPORATE SOURCE: Department of Microbiology and Cell Science, University of Florida, Gainesville 32611, USA.
CONTRACT NUMBER: CA 69959 (NCI)
SOURCE: JOURNAL OF INTERFERON AND CYTOKINE RESEARCH, (1997 Jan) 17 (1) 11-5.
Journal code: CD4. ISSN: 1079-9907.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707

AB Type I interferons (IFN), such as IFN-alpha, are potent antiproliferative and antitumor agents. IFN-tau, originally **identified** as a pregnancy recognition hormone, is a type I IFN that is related to IFN-alpha. We examine here the mechanism. . . IFN-alpha was more effective than IFN-tau in this regard. Both IFN were found to inhibit the kinase activity of the **cyclin**-dependent kinase cdk2 in a manner that correlated with their relative abilities to cause cells to accumulate in the G1 phase of the cell cycle. Further, IFN treatment did not affect the expression of cdk2 protein, suggesting that the IFN **modulated** cdk2 activity through a cdk inhibitor. Consistent with this conclusion, both IFN induced the expression of the **cyclin**-dependent kinase inhibitor protein **p21**. The levels of **p21** induced also correlated with the relative abilities of the IFN to inhibit cdk2 activity and to arrest cell growth in the G1 phase of the cell cycle. Moreover, following IFN treatment, increased levels of **p21** were found complexed with cdk2, consistent with its role in the inhibition of cdk2 activity. These data suggest that **p21**-mediated inhibition of cdk2 activity plays an important role in the antiproliferative activity of type I IFN. The findings highlight interesting. . .

L9 ANSWER 28 OF 37 MEDLINE
ACCESSION NUMBER: 97115887 MEDLINE
DOCUMENT NUMBER: 97115887
TITLE: The absence of p21Cip1/WAF1 alters keratinocyte growth and differentiation and promotes ras-tumor progression.
AUTHOR: Missero C; Di Cunto F; Kiyokawa H; Koff A; Dotto G P
CORPORATE SOURCE: Cutaneous Biology Research Center, Harvard Medical School, Massachusetts General Hospital, Charlestown 02129, USA.
CONTRACT NUMBER: AR39190 (NIAMS)
CA16038 (NCI)
SOURCE: GENES AND DEVELOPMENT, (1996 Dec 1) 10 (23) 3065-75.
Journal code: FN3. ISSN: 0890-9369.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199703
ENTRY WEEK: 19970303

AB p21Cip1/WAF1 was the first **cyclin**-dependent kinase (CDK) inhibitor to be **identified**, as a mediator of p53 in DNA damage-induced growth arrest, cell senescence, and direct CDK regulation. **p21** may also play an important role in differentiation-associated growth arrest, as its expression is augmented in many terminally differentiating cells. A general involvement of **p21** in growth/differentiation control and tumor suppression has been questioned, as mice lacking **p21** undergo a normal development, harbor no gross alterations in any of their organs, and exhibit no increase in spontaneous tumor. . . differentiation could be unmasked under conditions where normal homeostatic mechanisms are impaired. We report here that primary keratinocytes derived from **p21** knockout mice, transformed with a ras oncogene, and injected subcutaneously into nude mice exhibit a very aggressive tumorigenic behavior, which is not observed with wild-type control keratinocytes nor with keratinocytes with a disruption of the closely related p27 gene. **p21** knockout keratinocytes tested under well-defined in vitro conditions show a significantly increased proliferative potential, which is also observed but to a lesser extent with p27 knockout cells. More profound differences

were found in the differentiation behavior of **p21** versus p27 knockout keratinocytes, with **p21** (but not p27) deficiency causing a drastic down-**modulation** of differentiation markers linked with the late stages of the keratinocyte terminal differentiation program. Thus, our results reveal a so far undetected role of **p21** in tumor suppression, demonstrate that this function is specific as it cannot be attributed to the closely related p27 molecule, and point to an essential involvement of **p21** in terminal differentiation control, which may account for its role in tumor suppression.

L9 ANSWER 29 OF 37 MEDLINE
ACCESSION NUMBER: 97134670 MEDLINE
DOCUMENT NUMBER: 97134670
TITLE: A cyclin-dependent kinase inhibitor, Dacapo, is necessary for timely exit from the cell cycle during Drosophila embryogenesis.
AUTHOR: de Nooij J C; Letendre M A; Hariharan I K
CORPORATE SOURCE: Massachusetts General Hospital Cancer Center, Charlestown 02129, USA.
SOURCE: CELL, (1996 Dec 27) 87 (7) 1237-47.
Journal code: CQ4. ISSN: 0092-8674.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
OTHER SOURCE: GENBANK-U77937
ENTRY MONTH: 199704
ENTRY WEEK: 19970402
AB In a **screen** for genes that interact with the Rap1 GTPase, we have **identified** a Drosophila gene, dacapo (dap), which is a member of the **p21**/p27 family of cdk inhibitors. Unlike mammalian cdk inhibitors studied to date, dap is essential for normal embryonic development. Dacapo inhibits **cyclin**-cdk activity in vitro. Overexpressing dap during eye development interferes with cell cycle progression and interacts genetically with the retinoblastoma homolog (Rbf) and **cyclin** E. dap expression in embryos parallels the exit of cells from the cell cycle. dap mutant embryos delay the normal. . .

L9 ANSWER 30 OF 37 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1996:262760 BIOSIS
DOCUMENT NUMBER: PREV199698818889
TITLE: Human and plant proliferating-cell nuclear antigen have a highly conserved binding site for the p53-inducible gene product p21-WAF1.
AUTHOR(S): Ball, Kathryn L. (1); Lane, David P.
CORPORATE SOURCE: (1) CRC Cell Transformation Group, Dep. Biochem., Med. Sci.
Inst., Univ. Dundee, Dundee DD1 4HN UK
SOURCE: European Journal of Biochemistry, (1996) Vol. 237, No. 3, pp. 854-861.
ISSN: 0014-2956.
DOCUMENT TYPE: Article
LANGUAGE: English
AB. . . of a set of gene products that have a direct role in a DNA-damage-induced cell-cycle growth arrest. One such protein, **p21**-WAF1, has been shown to be essential for radiation-induced growth arrest.
There appear to be at least two cellular targets of **p21**-WAF1 during checkpoint control, the G-1-**cyclin**-dependent kinases (CDK) and proliferating-cell nuclear antigen (PCNA). The aim of the research reported here was to determine whether the interactions between the human growth inhibitor **p21**-WAF1 and PCNA from plants and humans are conserved. If so, this would suggest that **modulation** of PCNA activity may play an important role in plant responses. to DNA damage and would imply that functional homologue(s) of **p21**-WAF1

exist in plants. We show that the **p21**-WAF1-interaction domain of PCNA is conserved between humans and plants. A peptide that contains the site of human **p21**-WAF1 that binds human PCNA has been used to precipitate PCNA from crude pea (Pisum savitum) extracts. We used the **p21**-WAF1 peptide as an affinity matrix and showed that pea PCNA bound in a specific high-affinity manner. This finding was used. . . allowed PCNA from plant tissue to be purified to homogeneity. Pure pea PCNA forms a stable complex with full-length human **p21**-WAF1 and the specific amino acids of **p21**-WAF1 required for the interaction have been **identified**. The critical residues were identical to those required for binding to human PCNA, which indicates that the interaction of human **p21**-WAF1 with PCNA is highly conserved at each amino acid position between pea and human.

L9 ANSWER 31 OF 37 MEDLINE
ACCESSION NUMBER: 97094164 MEDLINE
DOCUMENT NUMBER: 97094164
TITLE: Adhesion-dependent control of cyclin E/cdk2 activity and cell cycle progression in normal cells but not in Ha-ras transformed NRK cells.
AUTHOR: Carstens C P; Kramer A; Fahl W E
CORPORATE SOURCE: McArdle Laboratory for Cancer Research, University of Wisconsin, Madison 53706, USA.
CONTRACT NUMBER: CA42024 (NCI)
P30-CA07175 (NCI)
SOURCE: EXPERIMENTAL CELL RESEARCH, (1996 Nov 25) 229 (1) 86-92. Journal code: EPB. ISSN: 0014-4827.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199703
ENTRY WEEK: 19970304
AB . . . adhesion of NRK fibroblasts to an appropriate surface leads to cell cycle arrest in late G1 and failure to produce **cyclin** A. Previously, we showed that adhesion-dependent expression of **cyclin** A is transcriptionally regulated. In an effort to **identify** elements of the adhesion-mediated signal transduction cascade upstream of **cyclin** A activation, we investigated the expression of **cyclin** E and its associated kinase activity in adherent and suspended NRK cells. Expression of **cyclin** E was found to be unaffected by suspension. However, **cyclin** E complexes immunoprecipitated from extracts prepared from NRK cells 12 h after release from G0 arrest were found to be catalytically inactive in suspended but not in adherent cells. This suspension-induced inhibition of **cyclin** E-associated kinase activity was not observed in NRK cells transformed by a c-Ha-ras oncogene containing a G12V mutation. When G0-synchronized NRK cells were transfected with a **cyclin** A promoter:luciferase reporter construct along with expression vectors for either wild-type cdk2 or a dominant-negative cdk2 mutant, transcriptional activation of **cyclin** A was found to be dependent on catalytically active cdk2. Inhibition of **cyclin** E/cdk2 complexes has frequently been attributed to association of the cdk inhibitors **p21**(Cip1) and p27(Kip1). However, no differences between adherent and suspended cells could be observed for either expression or cdk2 association of **p21**(Cip1) or p27(Kip1), nor were any proteins specifically associated with cdk2 or **cyclin** E in immunoprecipitates from metabolically labeled cell extracts. These results define a pathway through which an adhesion-generated signal controls **cyclin** A expression by **modulating cyclin** E/cdk2 activity.

L9 ANSWER 32 OF 37 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1995:348008 BIOSIS

DOCUMENT NUMBER: PREV199598362308
TITLE: The role of p53 in coordinated regulation of cyclin D1 and p21 gene expression by the adenovirus E1A and E1B oncogenes.
AUTHOR(S): Spitkovsky, Dimitry; Steiner, Philippe; Gopalkrishnan, Rahul V.; Eilers, Martin; Jansen-Durr, Pidder (1)
CORPORATE SOURCE: (1) Deutsches Krebsforschungszentrum, Agewandte Tumorvirol., Abt. 620, INF 242, D-69120 Heidelberg Germany
SOURCE: Oncogene, (1995) Vol. 10, No. 12, pp. 2421-2425. ISSN: 0950-9232.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Expression of the **cyclin** D1 gene is induced when quiescent fibroblasts are stimulated to reenter the cell cycle by addition of growth factors. Moderate ectopic expression of **cyclin** D1 in early G1 facilitates progression through G1. When transiently overexpressed at the G1/S boundary, **cyclin** D1 prevents S phase entry, suggesting a dual role for this protein in cellular growth control. It was shown that the retinoblastoma protein (pRB) can activate **cyclin** D1 gene expression; furthermore, there is evidence that expression of the **cyclin** D1 gene is down-regulated by the SV40 large T and adenovirus E1A genes, both of which were shown to target. . . report that in diploid human fibroblasts functional inactivation of pRB by adenovirus E1A is not sufficient for efficient repression of **cyclin** D1 gee expression, since the E1B gene product, in addition to E1A, is required for repression of the **cyclin** D1 gene. Since E1B was shown to target p53, we investigated the role of p53 for expression of the **cyclin** D1 gene. In a cell line with temperature-sensitive p53, **cyclin** D1 is moderately expressed at the restrictive temperature. Induction of p53 function by temperature shift leads to an increase of **cyclin** D1 mRNA and protein, parallel to the activation of **p21**-WAF-1/CIP1 gene expression in this system. When the capability of adenovirus gene products to affect expression of either gene was analysed, we found that infection of Ad5 drastically reduced **cyclin** DI and **p21**-WAF-1/CIP1 gene expression in cells where p53 function is limiting. Under these conditions E1A and E1B cooperate to reduce the **cyclin** D1 level, while **p21**-WAF-1/CIP1 expression was found insensitive to E1A expression. In cells containing elevated p53 function, **modulation** of gene expression by E1B was severely compromised; under these conditions, expression of EIA reduced expression of **cyclin** D1 without affecting **p21**-WAF-1/CIP1. The data suggest that E1A and E1B cooperate to inhibit expression of **cyclin** D1 and **identify** the **cyclin** D1 gene as a new downstream target for p53.

L9 ANSWER 33 OF 37 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1996:16625 BIOSIS
DOCUMENT NUMBER: PREV199698588760
TITLE: Gadd45 is a nuclear cell cycle regulated protein which interacts with p21-Cip1.
AUTHOR(S): Kearsey, Jonathan M.; Coates, Philip J.; Prescott, Alan R.; Warbrick, Emma; Hall, Peter A. (1)
CORPORATE SOURCE: (1) Dep. Pathol., Univ. Dundee, Dundee, Scotland DD1 9SY UK
SOURCE: Oncogene, (1995) Vol. 11, No. 9, pp. 1675-1683. ISSN: 0950-9232.
DOCUMENT TYPE: Article
LANGUAGE: English
AB GADD45 was originally **identified** as a cDNA clone induced by growth arrest and DNA damage. We show that Gadd45 is a nuclear protein, widely. . . of Gadd45 from mammalian cells reveals that it is tightly associated with a protein which reacts with antibodies to the

cyclin dependent kinase inhibitor **p21**-Cip1. Binding of recombinant Gadd45 protein to overlapping **p21**-Cip1 peptides in ELISA assays and use of the yeast two hybrid assay show that Gadd45 directly interacts with this cell. . . Gadd45 may act in the regulation of the cell cycle. It is postulated that the interactions of Gadd45 with both **p21**-Cip1 and PCNA are important for the **modulation** of cell cycles, and for the inhibition of DNA replication.

L9 ANSWER 34 OF 37 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95109914 EMBASE
DOCUMENT NUMBER: 1995109914
TITLE: [New cell-cycle regulators: The cdk-cyclins modulatory proteins].
DE NOUVEAUX REGULATEURS DU CYCLE CELLULAIRE: LES PROTEINES MODULATRICES DES COMPLEXES CDK-CYCLINES.
AUTHOR: Darbon J.-M.; Fesquet D.; Cavadore J.-C.
CORPORATE SOURCE: Inserm U 326, CHU Purpan,31053 Toulouse Cedex, France
SOURCE: Medecine/Sciences, (1995) 11/3 (349-356).
ISSN: 0767-0974 CODEN: MSMSE4
COUNTRY: France
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: French
SUMMARY LANGUAGE: French; English
AB A few years after **identification** of the universal factor that controls onset of mitosis in all eukaryotic cells, MPF (M-phase promoting factor), as the **cyclin** B-cdc2 kinase, it has become apparent that all transitions of the cell cycle are controlled by a series of kinase complexes between cdc2-related **cyclin**-dependent kinases (cdk) and their respective regulatory **cyclin** subunits. While the phosphorylation of Thr161 in cdc2 (or its homologue in the other cdks) appears as a prerequisite for maximal activity of the **cyclin** -kinases, phosphorylation on Thr14 and Tyr15 exerts an inhibitory action on **cyclin** B-cdc2 but likely not on the other complexes in vivo. A recent flurry of reports reveals the existence of a variety of small proteins which bind to and **modulate** G1/S cdk-**cyclin** complexes. In mammalian cells, 5 different regulators, p15, p16, **p21**, p24 and p27, have been **identified** so far, being mainly inhibitors. They are believed to delay activation of cdk-**cyclins** to maintain a temporal order of cdk activation during progression of G1. Some of these inhibitors have been shown to be particularly involved in certain circumstances: **p21**, whose synthesis is induced by p53, causes G1 cell-cycle arrest following DNA damage or in senescent or quiescent cells. These effects seem essentially the consequence of the inhibitory action of **p21** on cdk2-**cyclin** E complexes but **p21** is possibly a universal cdk-**cyclin** regulator. p27 induces G1 arrest in contact-inhibited and in TGF.beta.- or cyclic AMP-treated cells by inhibiting particularly cdk2-**cyclin** E and/or cdk4-**cyclin** D. p15, whose synthesis is induced by TGF.beta., and p16 bind cdk4 as well as cdk6 and appear as new.
. .

L9 ANSWER 35 OF 37 MEDLINE
ACCESSION NUMBER: 95095079 MEDLINE
DOCUMENT NUMBER: 95095079
TITLE: Growth suppression by p18, a p16INK4/MTS1- and p14INK4B/MTS2-related CDK6 inhibitor, correlates with wild-type pRb function.
AUTHOR: Guan K L; Jenkins C W; Li Y; Nichols M A; Wu X; O'Keefe C L; Matera A G; Xiong Y
CORPORATE SOURCE: Department of Biological Chemistry, University of Michigan,
Ann Arbor 48109-0606..

CONTRACT NUMBER: GM 51586 (NIGMS)
SOURCE: GENES AND DEVELOPMENT, (1994 Dec 15) 8 (24) 2939-52.
Journal code: FN3. ISSN: 0890-9369.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U17074; GENBANK-U17075
ENTRY MONTH: 199503

AB The D-type **cyclin**-dependent kinases CDK4 and CDK6 are complexed with many small cellular proteins (p14, p15, p16, p18, and p20). We have isolated. . . corresponding to the MTS2 genomic fragment that encodes the CDK4- and CDK6-associated p14 protein. By use of a yeast interaction **screen** to search for CDK6-interacting proteins, we have also **identified** an 18-kD human protein, p18, that is a homolog of the **cyclin** D-CDK4 inhibitors p16 (INK4A/MTS1) and p14 (MTS2/INK4B). Both in vivo and in vitro, p18 interacts strongly with CDK6, weakly with CDK4, and exhibits no detectable interaction with the other known CDKs. Recombinant p18 inhibits the kinase activity of **cyclin** D-CDK6. Distinct from the **p21**/p27 family of CDK inhibitors that form ternary complexes with **cyclin**-CDKs, only binary complexes of p14, p16, and p18 were found in association with CDK4 and/or CDK6. Ectopic expression of p18. . .

L9 ANSWER 36 OF 37 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1994:534474 BIOSIS
DOCUMENT NUMBER: PREV199497547474
TITLE: A molecular definition of terminal cell differentiation in human melanoma cells.
AUTHOR(S): Jiang, Hongping; Lin, Jian; Fisher, Paul B. (1)
CORPORATE SOURCE: (1) Dep. Pathol. Urol., Comprehensive Cancer Cent./Inst. Cancer Res., Columbia Univ., Coll. Phys. Surg., PH STEM-10, 630 W. 168th St., New York, NY 10032 USA
SOURCE: Molecular and Cellular Differentiation, (1994) Vol. 2, No. 3, pp. 221-239.
ISSN: 1065-3074.
DOCUMENT TYPE: General Review
LANGUAGE: English

AB. . . and express differentiation-related functions or irreversibly terminally differentiate by treatment with appropriate agents. This system represents a useful model for **identifying** and defining the roles of cellular genes in regulating growth, mediating specific biochemical pathways in differentiation, and inducing the irreversible loss of proliferative capacity associated with terminal cell differentiation. Using subtraction hybridization, cDNA clones have been **identified** that display differential expression as a function of growth arrest, treatment with chemotherapeutic and DNA-damaging agents, and terminal cell differentiation.. . . differentially expressed cDNAs have been termed melanoma differentiation-associated (mda) genes (41). Six cDNAs have been cloned during the initial library **screening** that represent differentially expressed genes not previously reported or ascribed specific functions and may therefore represent novel genes involved in.

. differentiation (41). One initially novel cDNA, mda-6, that displays increased expression in terminally differentiated human melanoma cells is identical to **p21**, a **cyclin**-dependent kinase inhibitor (47). **p21** is a critical cell cycle-regulating gene that has been cloned by a number of laboratories using different approaches and referred. . . WAF1 (49), and sdi1 (51). Our current approach, induction of terminal differentiation combined with subtraction hybridization, has proven useful for **identifying** genes critical to the maintenance

of normal cellular physiology (growth, differentiation, and response to DNA damage) and genes relevant to. . .

L9 ANSWER 37 OF 37 MEDLINE
ACCESSION NUMBER: 94306519 MEDLINE
DOCUMENT NUMBER: 94306519
TITLE: p27, a novel inhibitor of G1 cyclin-Cdk protein kinase activity, is related to p21.
AUTHOR: Toyoshima H; Hunter T
CORPORATE SOURCE: Molecular Biology and Virology Laboratory, Salk Institute, La Jolla, California 92037.
CONTRACT NUMBER: CA14195 (NCI)
CA39780 (NCI)
SOURCE: CELL, (1994 Jul 15) 78 (1) 67-74.
Journal code: CQ4. ISSN: 0092-8674.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
OTHER SOURCE: GENBANK-U10440
ENTRY MONTH: 199410
AB Using a yeast interaction **screen** to search for proteins that interact with **cyclin** D1-Cdk4, we **identified** a 27 kDa mouse protein related to the **p21 cyclin**-Cdk inhibitor. p27 interacts strongly with D-type **cyclins** and Cdk4 in vitro and more weakly with **cyclin** E and Cdk2. In mouse fibroblasts, p27 is associated predominantly with **cyclin** D1-Cdk4. Recombinant p27 is a potent inhibitor of **cyclin** D1-Cdk4 and **cyclin** A-Cdk2 protein kinase activity and a weaker inhibitor of **cyclin** B1-Cdc2. Overexpression of p27 in Saos-2 cells causes G1 arrest. p27 protein levels do not change as serum-stimulated quiescent mouse fibroblasts progress through the cell cycle. p27 is identical to p27Kip1, a **cyclin**-Cdk inhibitor present in TGF beta-treated cells. p27 has the hallmarks of a negative regulator of G1 progression and may mediate. . .

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